



B5

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 263/24, A61K 31/425 C07D 413/06, 311/58 A01N 31/35, C07D 263/56 C07C 59/64, 69/612	A1	(11) International Publication Number: WO 91/19702 (43) International Publication Date: 26 December 1991 (26.12.91)
(21) International Application Number: PCT/US91/03858 (22) International Filing Date: 31 May 1991 (31.05.91) (30) Priority data: 537,673 14 June 1990 (14.06.90) US (60) Parent Application or Grant (63) Related by Continuation US 537,673 (CIP) Filed 14 June 1990 (14.06.90) (71) Applicant (for all designated States except US): PFIZER INC. [US/US]; Eastern Point Road, Groton, CT 06340 (US).	(72) Inventor; and (75) Inventor/Applicant (for US only) : HULIN, Bernard [FR/US]; 8 High Street, Essex, CT 06426 (US). (74) Agents: LUMB, J., Trevor et al.; Pfizer Inc., Eastern Point Road, Groton, CT 06340 (US). (81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent), US. Published With international search report.	
(54) Title: 3-ARYL-2-HYDROXYPROPIONIC ACID DERIVATIVES AND ANALOGS AS HYPOGLYCEMIC AGENTS (57) Abstract Certain 3-(phenyl, chroman-2-yl, benzofuran-5-yl or benzoxazole-5-yl)-2-(hydroxy or mercapto)propionic acid derivatives and analogs are useful as hypoglycemic and hypocholesterolemic agents.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TC	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark				

-1-

3-ARYL-2-HYDROXYPROPIONIC ACID DERIVATIVES
AND ANALOGS AS HYPOGLYCEMIC AGENTS

Background of the Invention

5 The present invention relates to certain compounds of the formulas (I) and (II), depicted below, having utility as hypoglycemic and hypocholesterolemic agents, methods for their use and pharmaceutical compositions containing them.

10 In spite of the early discovery of insulin and its subsequent wide-spread use in the treatment of diabetes, and the later discovery and use of sulfonylureas (e.g. chlorpropamide, tolbutamide, acetohexamide, tolazamide) and biguanides (e.g.
15 phenformin) as oral hypoglycemic agents, the treatment of diabetes remains less than satisfactory. The use of insulin, necessary in about 10% of diabetic patients in which synthetic hypoglycemic agents are not effective (Type I diabetes, insulin dependent diabetes mellitus),
20 requires multiple daily doses, usually by self injection. Determination of the proper dosage of insulin requires frequent estimations of the sugar in the urine or in the blood. The administration of an excess dose of insulin causes hypoglycemia, with
25 effects ranging from mild abnormalities in blood glucose or coma, or even death. Treatment of non-insulin dependent diabetes mellitus (Type II diabetes) usually consists of a combination of diet, exercise, oral agents, e.g., sulfonylureas, and in more
30 severe cases, insulin. However, the clinically available hypoglycemics are unfortunately fraught with other toxic manifestations which limit their use. In any event, where one of these agents may fail in an individual case, another may succeed. A continuing

-2-

need for hypoglycemic agents, which may be less toxic or succeed where others fail, is clearly evident.

Furthermore, atherosclerosis, a disease of the arteries, is recognized to be the leading cause of death in the United States and Western Europe. The pathological sequence leading to atherosclerosis and occlusive heart disease has been described in detail by Ross and Glomset in New England Journal of Medicine 295, 369-377 (1976). The earliest stage in this sequence is the formation of "fatty streaks" in the carotid, coronary and cerebral arteries and in the aorta. These lesions are yellow in color due to the presence of lipid deposits found principally within smooth-muscle cells and in macrophages of the intima layer of the arteries and aorta. Cholesterol and cholesteryl ester account for most of this lipid. Further, it is postulated that most of the cholesterol found within the fatty streaks results from uptake from the plasma. These fatty streaks, in turn, give rise to development of the "fibrous plaque", which consists of accumulated intimal smooth muscle cells laden with lipid and surrounded by extra cellular lipid, collagen, elastin and proteoglycans. The cells plus matrix form a fibrous cap that covers a deeper deposit of cell debris and more extracellular lipid. The lipid is primarily free and esterified cholesterol. The fibrous plaque forms slowly, and is likely in time to become calcified and necrotic, advancing to the "complicated lesion" which accounts for the the arterial occlusion and tendency toward mural thrombosis and arterial muscular spasm that characterize advanced atherosclerosis.

-3-

Epidemiological evidence has firmly established hyperlipidemia as a primary risk factor in causing cardiovascular disease (CVD) due to atherosclerosis.

5 In recent years, leaders of the medical profession have placed renewed emphasis on lowering plasma cholesterol levels, and low density lipoprotein cholesterol in particular, as an essential step in prevention of CVD. The upper limits of "normal" are now known to be significantly lower than heretofore appreciated. As a
10 result, large segments of Western populations are now realized to be at high risk for development or progression of CVD because of this factor. Individuals who possess independent risk factors in addition to
15 hyperlipidemia are at particularly high risk. Such independent risk factors include glucose intolerance, left ventricular hypertrophy hypertension, and being of the male sex. Cardiovascular disease is especially prevalent among diabetic subjects, at least in part
20 because of the existence of multiple independent risk factors. Successful treatment of hyperlipidemia in the general population, and in diabetic subjects in particular, is therefore of exceptional medical importance.

25 The first step in recommended therapeutic regimens for hyperlipidemia is dietary intervention. While diet alone produces adequate response in some individuals, many others remain at high risk and must be treated further by pharmacological means. New drugs for the
30 treatment of hyperlipidemia are, therefore, of great potential benefit for large numbers of individuals at high risk of developing CVD. Further, successful treatment of both the hyperlipidemia and hyperglycemia

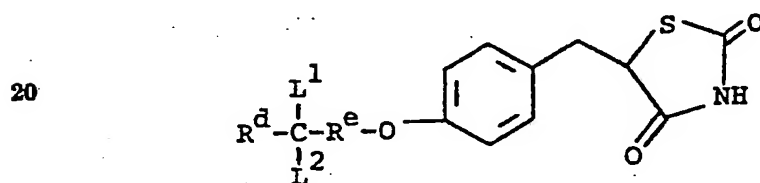
-4-

associated with the diabetic state with a single therapeutic agent is particularly desirable.

5 In addition to the hypoglycemic agents cited above, a variety of other compounds have been reported to possess this type of activity, as reviewed by Blank [Burger's Medicinal Chemistry, Fourth Edition, Part II, John Wiley and Sons, N.Y. (1979), pp. 1057-1080].

10 Schnur, in U.S. Patents 4,342,771, 4,367,234 and 4,617,312, discloses various hypoglycemic oxazolidine-2,4-diones and thiazolidine-2,4-diones substituted at the 5-position with aryl or heteroaryl groups.

15 Kawamatsu et al., U.S. Patent 4,340,605, disclose hypoglycemic thiazolidine-2,4-dione compounds of the formula

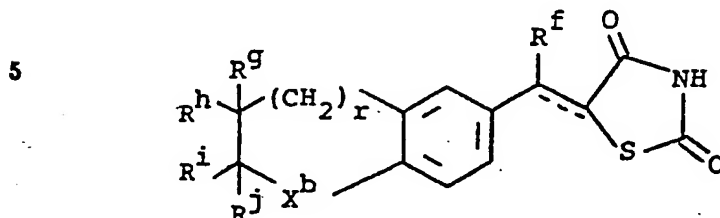


25 wherein R^e is a bond or lower alkylene and when R^d is an optionally substituted five- or six-membered heterocyclic group including one or two hetero-atoms selected from N, O and S, L^1 and L^2 may each be defined as hydrogen. See also Sohda et al., Chem., Pharm. Bull. Japan, Vol. 30, pp. 3580-3600 (1982).

30

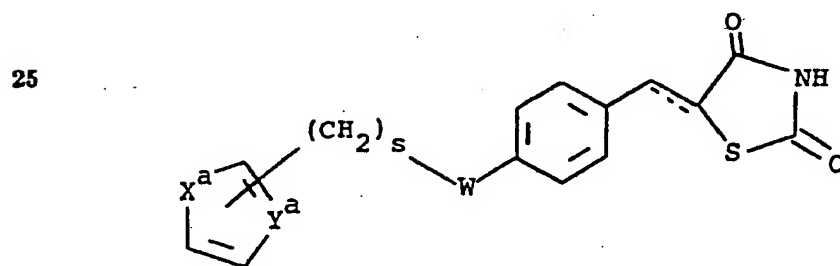
-5-

Eggler et al., U.S. Patent 4,703,052, disclose hypoglycemic thiazolidinediones of the formula



10 where the dotted line represents an optional bond, R^f is H, methyl or ethyl, X^b is O, S, SO, SO_2 , CH_2 , CO, CHOH or NR^k , R^k is H or an acyl group and the numerous definitions of R^g , R^h , R^i and R^j include R^g , R^h and R^i as hydrogen or methyl and R^j as optionally substituted
15 phenyl, benzyl, phenethyl or styryl. EP 283,035A and EP 299,620A describe structurally related benzoxazole and benzofuran derivatives as antidiabetic agents.

Clark et al., in published World patent applications WO89/08650, WO89/8651 and WO89/08652
20 disclose hypoglycemic thiazolidinediones which collectively include compounds of the type:



30

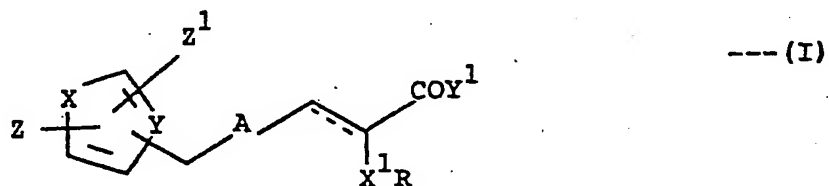
wherein ---- represents a bond or no bond; W is O, CO, CH_2 , CHOH, or $-CH=CH-$; s is 0, 1 or 2; X^a is S, O, NR^a , $-CH=CH-$, $-CH=N-$ or $-N=CH-$; and Y^a is CH or N.

-6-

Summary of the Invention

The present invention is directed to compounds having the formulas

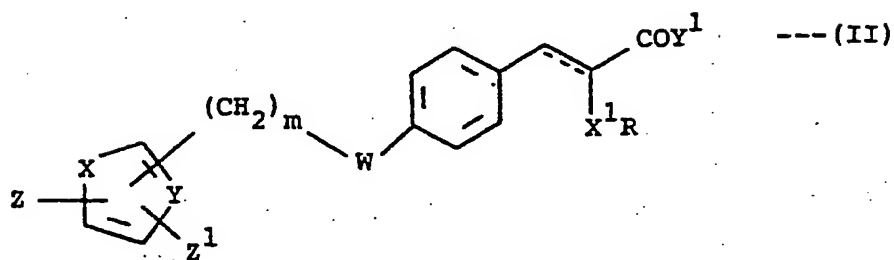
5



10

and

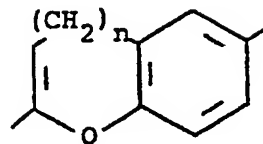
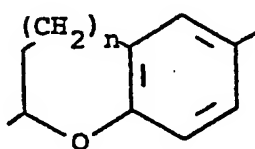
15



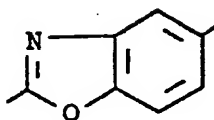
20

wherein A is

25



or



30

n is 0 or 1;

m is 0, 1 or 2;

---- represents a bond or no bond;

-7-

R is (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl,
(C₃-C₈)alkenyl, (C₃-C₈)alkynyl, phenyl,
(C₇-C₈)phenylalkyl, (C₂-C₈)alkanoyl, or one of said
5 groups mono- or disubstituted with (C₁-C₃)alkyl,
trifluoromethyl, hydroxy, (C₁-C₃)alkoxy, fluoro or
chloro;

W is O, CO, CH₂, CHOH or -CH=CH-;

X is S, O, NR², -CH=CH-, -CH=N- or -N=CH-;

R² is hydrogen, (C₁-C₃)alkyl, phenyl or benzyl;

10 Y is CH or N;

Z is H, amino, (C₁-C₇)alkyl, (C₃-C₇)cycloalkyl,
phenyl, or phenyl mono- or disubstituted with
(C₁-C₃)alkyl, trifluoromethyl, (C₁-C₃)alkoxy, phenyl,
15 phenoxy, benzyl, benzyloxy, fluoro or chloro;

Z¹ is hydrogen or (C₁-C₃)alkyl;

X¹ is O, S, SO or SO₂; and

Y¹ is hydroxy, (C₁-C₃)alkoxy, phenoxy, benzyloxy,
amino, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanesulfonyl-
20 amino, benzenesulfonylamino, naphthalenesulfonylamino,
di[(C₁-C₃)alkyl]aminosulfonylamino, or one of said
groups mono- or disubstituted with (C₁-C₃)alkyl,
trifluoromethyl, hydroxy, (C₁-C₃)alkoxy, fluoro or
chloro;

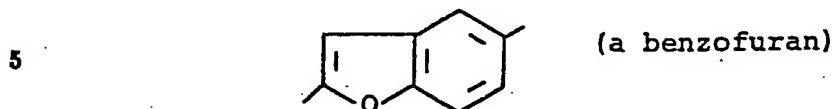
25 the pharmaceutically-acceptable cationic salts
thereof when Y¹ is hydroxy; and

the pharmaceutically-acceptable acid addition
salts thereof when the compound contains a basic
nitrogen atom.

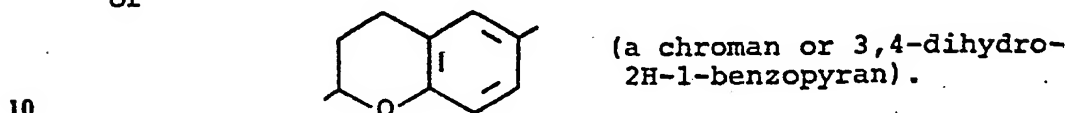
30

-8-

In the preferred compounds, the dotted line (----) represents no bond. The preferred values of A are



or



15 The preferred values of W are O or CO. In their preferred values, X, Y, Z and Z¹ are taken in such manner as to form a 5-methyl-2-phenyloxazol-4-yl group.

20 In those compounds in which ---- is not a bond, the carbon atom substituted by X¹R and COY¹ is asymmetric, such that these compounds can be either racemic or optically active. Resolution of a racemic form into a pair of optically active enantiomers is exemplified below, and the present invention is not to be narrowly construed as limited to the racemic form of these compounds. Similarly, those compounds of the formula (I) wherein the group A contains a saturated ring possess an asymmetric carbon at position 2; and

25 those compounds of the formula (II) contain an asymmetric carbon when W is CHOH.

30 The expression "pharmaceutically-acceptable cationic salts" is intended to define but not limited to such salts as the alkali metal salts, (e.g. sodium and potassium), alkaline earth metal salts (e.g. calcium and magnesium), aluminum salts, ammonium salts, and salts with organic amines such as benzathine

-9-

(N,N'-dibenzylethylenediamine), choline, diethanol-
amine, ethylenediamine, meglumine (N-methylglucamine),
benethamine (N-benzylphenethylamine) diethylamine,
piperazine, tromethamine (2-amino-2-hydroxymethyl-
1,3-propanediol) and procaine. An especially preferred
such salt is the sodium salt.

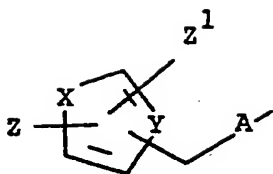
The expression "pharmaceutically-acceptable acid
addition salts" is intended to define but not limited
to such salts as the hydrochloride, hydrobromide,
sulfate, hydrogen sulfate, phosphate, hydrogen
phosphate, dihydrogenphosphate, acetate, succinate,
citrate, methanesulfonate (mesylate) and p-toluene-
sulfonate (tosylate) salts.

Also embraced by the present invention are pharma-
ceutical compositions for use in treating a
hyperglycemic mammal or a hypercholesterolemic mammal
which comprises a blood glucose lowering amount or a
blood cholesterol lowering amount of a compound of
formula (I) or (II) and a pharmaceutically-acceptable
carrier. The invention further comprises a method of
lowering blood glucose in a hyperglycemic mammal which
comprises administering to said mammal a blood glucose
lowering effective amount of a compound of formula (I)
or (II); and a method of lowering blood cholesterol in
a hypercholesterolemic mammal which comprises
administering to said mammal a blood cholesterol
lowering amount of a compound of the formula (I) or
(II).

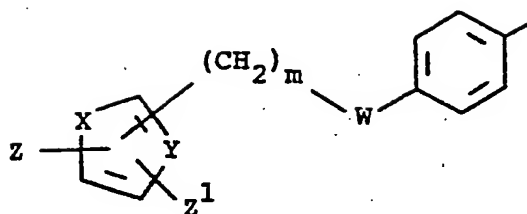
Detailed Description of the Present Invention

The compounds of the formulas (I) and (II) of the
present invention are readily prepared using
conventional chemical processes. In the discussion
which follows, the radical R' is defined as follows:

-10-

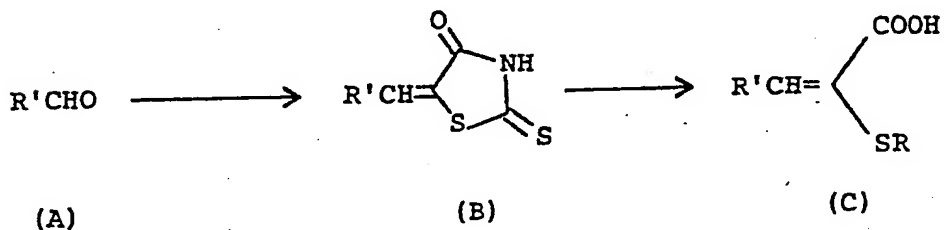


and



wherein m, A, W, X, Y, Z and Z¹ are as defined above.

20 When the dotted line (----) represents a bond, the compounds of the formula (I) or (II) wherein Y¹ is hydroxy and X¹ is S are generally prepared from the corresponding aldehyde by the two step sequence:



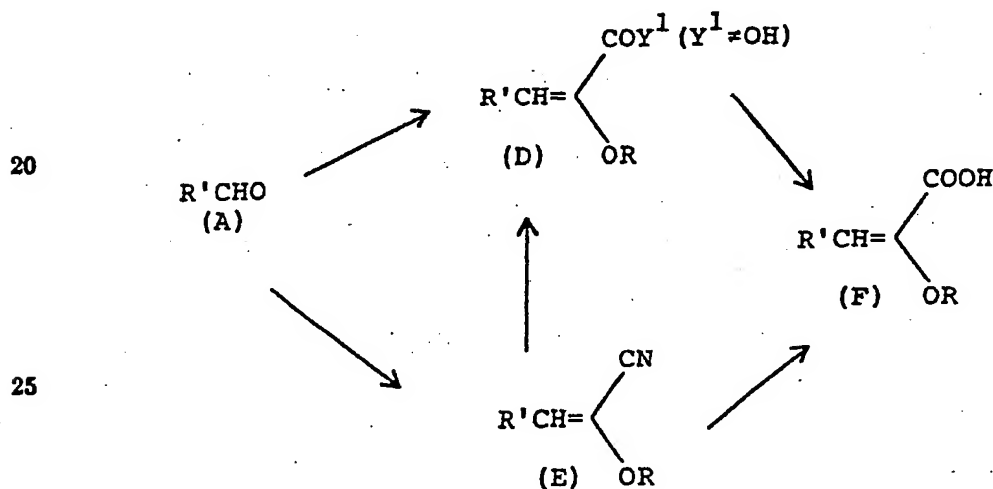
The first step of this sequence is accomplished by condensation of the aldehyde (A) with thiazolidine-4-one-2-thione (rhodanine) in the presence of a

-11-

secondary amine such as piperidine or pyrrolidine in a reaction inert solvent such as ethanol at a temperature in the range of about 40-100°C, conveniently at the reflux temperature of the reaction.

As used above and elsewhere herein, the expression "reaction inert solvent" refers to a solvent which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

When the dotted line (----) represents a bond, the compounds of the formula (I) or (II) wherein X^1 is O are generally prepared by condensation of the above aldehyde (A) with a suitably substituted acetic acid derivative, for example,



The condensation step is conveniently carried out by irreversibly converting the acrylic acid derivative, $CH_2=CH-COR$ or $CH_2=CH-COY^1$ (in which Y^1 is other than OH), to the sodium salt by the action of NaH in a reaction-inert solvent such as dimethylformamide, generally done at a temperature in the range of about

-12-

25-60°C, and then adding the aldehyde and further reacting, generally at a somewhat higher temperature, e.g., 50-100°C.

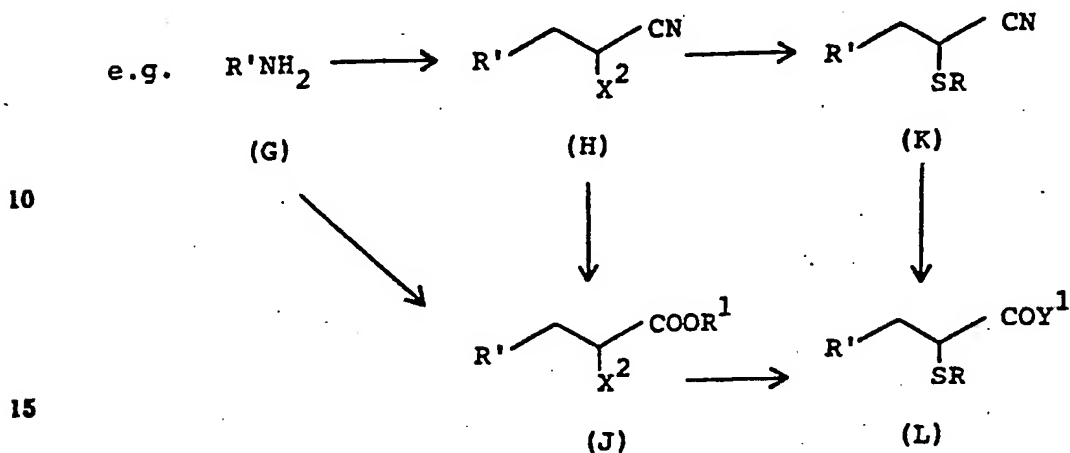
5 If the condensation product is an ester or an amide (D), it can, if desired, be conventionally hydrolyzed, preferably under aqueous basic conditions, to the acid. If the condensation product is a nitrile, it can be conventionally converted to ester, amide or acid, as desired. Specifically exemplified below is
10 the conversion of nitrile to carboxamide, from which both of the expected (E) and (Z) isomers about the double bond are isolated.

The compounds (C) and (F) are further converted to
15 compounds in which Y^1 is other than hydroxy by conventional transformations according to which acids are converted to esters, amides and imides. Furthermore, the double bond in such compounds can be conventionally reduced to form compounds of the
20 formulas (I) and (II) wherein the dotted line (----) represents no bond. For example, reduction of the double bond is accomplished by conventional hydrogenation over a noble metal catalyst such as Pd/C, Rh/C or $Rh(Ph_3P)_3Cl$ in a reaction inert solvent such as
25 ethanol generally at temperatures in the range of ambient to 80°C, preferably at moderate pressures, e.g., up to about 125 psig so as not to require expensive and complex high pressure hydrogenation apparatus. However, the presently preferred routes to
30 compounds of the formulas (I) and (II) wherein ---- represents no bond are as detailed below.

-13-

Compounds of the formulas (I) and (II) wherein the dotted line (----) represents no bond and X^1 is S are generally prepared from the corresponding amine via a two- or three-step reaction sequence:

5



wherein R, R' and Y^1 are as defined above, X^2 is a nucleophilically displacable group such as I, Cl, Br or OSO_2CH_3 , and R^1 is an ester forming group such as (C_1-C_3) alkyl. According to this sequence, the amine (G) is first conventionally diazotized (e.g. with $NaNO_2$ /conc.HBr or t-butyl nitrite) in the presence of a copper (II) salt and acrylonitrile or an acrylate ester to form the nitrile (H) or ester (J). This is followed by convention nucleophilic displacement of the group X^2 with RS^- , with or without conventional concurrent hydrolysis of the nitrile or ester. For example, an alpha-bromo ester (J, $X^2=Br$) is reacted with an excess of an alkali metal salt of a mercaptan or thiolcarboxylic acid (greater than two molar

20

25

30

-14-

equivalents) in an aqueous solvent such as aqueous dimethylformamide, usually at an elevated temperature, e.g., in the range of 60-100°C, to form the acid:



On the other hand, the nitrile or ester group is retained intact by reacting a compound (H) or (J) with a mercaptan or thiolcarboxylic acid in the presence of a base such as K_2CO_3 in an anhydrous reaction inert solvent such as dimethylformamide, generally at lower temperatures, e.g., in the range of about 15-45°C. Prior to or after nucleophilic displacement, nitrile groups are converted to desired groups $-\text{COY}^1$ by conventional methods. For example, compounds wherein Y^1 is alkoxy are obtained by contacting the nitrile with dry HCl in an excess of the corresponding alkanol, a reaction usually carried out without additional solvent at a temperature in the range of about 15-45°C.

Compounds of the formulas (I) and (II) wherein the dotted line (----) represents no bond and X^1 is O are generally prepared from the corresponding aldehyde according the following reaction sequences:

-15-

5

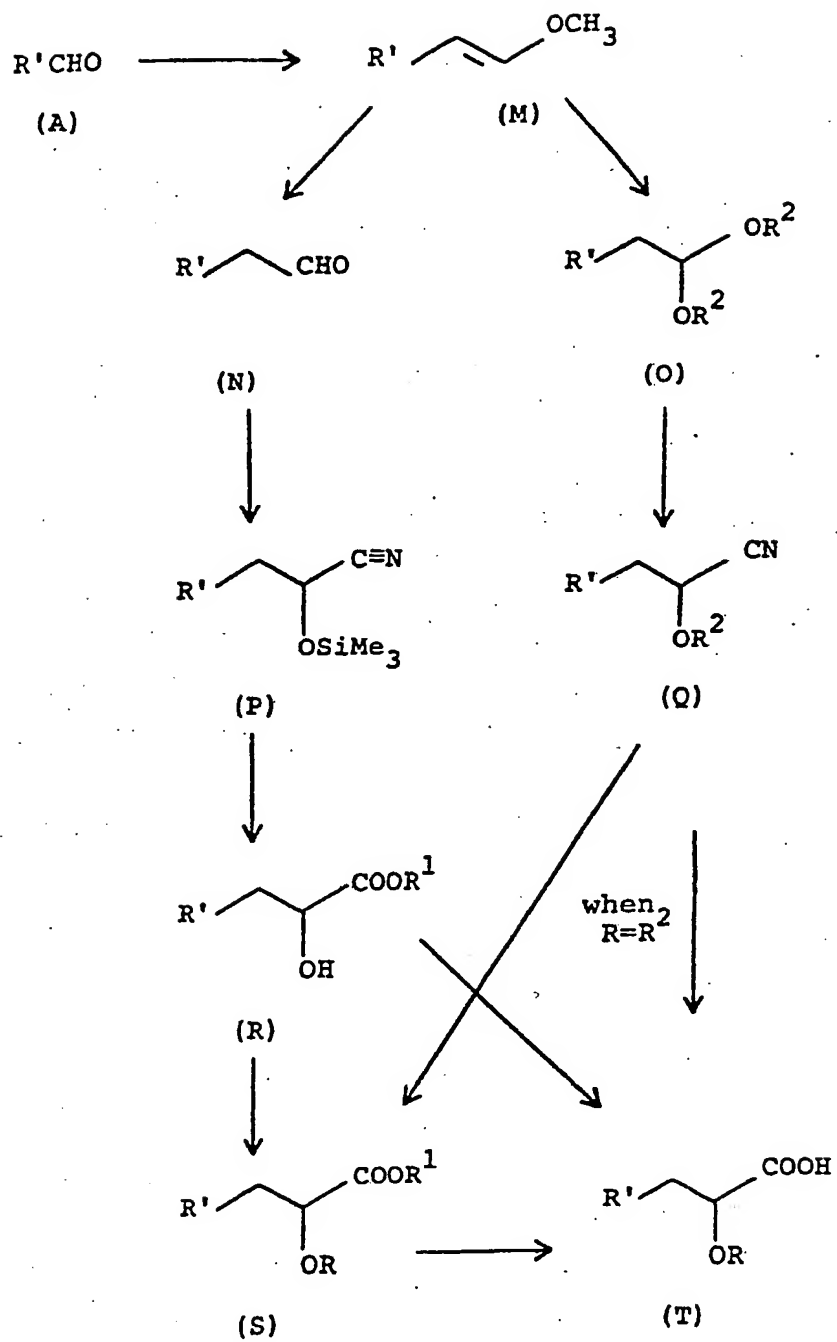
10

15

20

25

30



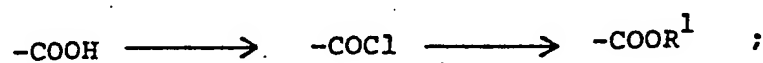
-16-

The enol ether (M) is conventionally formed from the aldehyde (A) via the Wittig reaction, using conditions as exemplified in specific examples below. In one
5 further sequence, the enol ether is conventionally hydrolyzed with aqueous acid to form the aldehyde (N), which in turn is reacted with trimethylsilyl cyanide to form the O-trimethylcyanhydrin (P). The latter is conventionally reacted with an alcohol R^1OH in the
10 presence of anhydrous HCl to form the alpha-hydroxy ester (R). When RO is an ester, e.g., acetoxy, the hydroxyester (R) is readily converted to the ester by the action of the appropriate activated acid, e.g., an acid chloride or mixed anhydride, in the presence of at
15 least one equivalent of a tertiary amine, usually in a reaction inert solvent such as tetrahydrofuran, conveniently at or near ambient temperature. When RO is an ether, e.g., ethoxy, the hydroxy ester (R) is reacted with NaH, under scrupulously anhydrous
20 conditions in a reaction inert solvent such as tetrahydrofuran, so as to irreversibly form the sodium salt. The latter is then coupled with a mesylate ester or halide in typical nucleophilic displacement conditions described above, under the same anhydrous
25 conditions to form the ester (S). Alternatively, under hydrous conditions (with at least one molar equivalent of water present), the latter reaction yields the acid (T). In a second further sequence, the enol ether (M) is reacted under anhydrous conditions with an alcohol
30 R^2OH in the presence of a strong anhydrous acid (e.g., p-toluenesulfonic acid) to form the acetal (O), which, upon reaction with trimethylsilyl cyanide, produces the cyanhydrin derivative (Q). The CN group in the latter compound is conventionally converted to the acid (T),

-17-

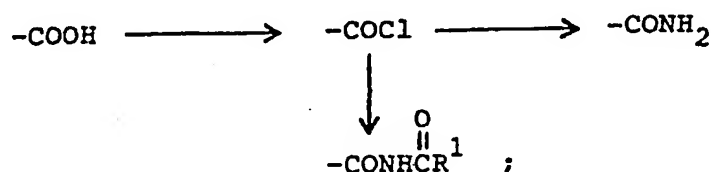
e.g. by the action of NaOH in an aqueous solvent, or to the ester (S), e.g., by the action of dry HCl in an excess of an alcohol R^1OH .

5 Many of the compounds of the present invention are alternatively or preferably prepared from preformed compounds having different values of R, X^1 and Y^1 . For example, sulfoxides ($X^1=SO$) are preferably formed from the corresponding sulfide ($X^1=S$) by the action of
10 substantially one molar equivalent of a peroxyacid, conveniently, m-chloroperbenzoic acid. Sulfones ($X^1=SO_2$) are also obtained from the corresponding sulfide, but now generally with an excess (at least 2 molar equivalents) of the peracid. These oxidations
15 are generally carried out in a reaction inert solvent such as tetrahydrofuran, at a temperature generally in the range of about 0-40°C. Other transformations conveniently carried out to convert one preformed compound of the formula (I) or (II) to another such
20 compound include esterification of acids, e.g.,



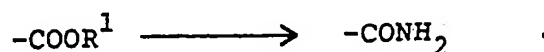
conversion of acids to amides or imides, e.g.,

25



30

and ammonolysis of esters, e.g.,



-18-

Various of these transformations are exemplified below.

It will be readily understood by those skilled in the organic chemical art that in the compounds of the formulas (I) and (II) in which the dotted line (----) represents no bond, the carbon atom bearing the X^1R and COY^1 groups is asymmetric and so potentially resolvable into a pair of optically active isomers. Substrates particularly well suited to such resolution are those carboxylic acids of the formulas (I) or (II) wherein Y^1 is OH, e.g., by combining the acid with an optically active amine, and separating the resulting pair of diastereomeric salts by fractional crystallization converting; or by reacting the acid with an optically alcohol or amine, and separating the resulting pair of diastereomeric esters or amides by chromatography or fractional crystallization, followed by hydrolysis of the separated isomers to yield the desired optically active acids. Such a resolution is exemplified below.

The pharmaceutically-acceptable cationic salts of the compounds of the present invention are readily prepared by reacting the acid forms with an appropriate base, usually one equivalent, in a co-solvent. Typical bases are sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium methoxide, magnesium hydroxide, calcium hydroxide, benzathine, choline, diethanolamine, piperazine and tromethamine. The salt is isolated by concentration to dryness or by addition of a non-solvent. In many cases, salts are preferably prepared by mixing a solution of the acid with a solution of a different salt of the cation (sodium or potassium ethylhexanoate, magnesium oleate), employing a solvent (e.g., ethyl acetate) from which the desired cationic salt precipitates, or can be

-19-

otherwise isolated by concentration and/or addition of a non-solvent.

5 The acid addition salts of the compounds of the present invention are readily prepared by reacting the base forms with the appropriate acid. When the salt is of a monobasic acid (e.g., the hydrochloride, the hydrobromide, the p-toluenesulfonate, the acetate), the hydrogen form of a dibasic acid (e.g., the hydrogen sulfate, the succinate) or the dihydrogen form of a tribasic acid (e.g., the dihydrogen phosphate, the citrate), at least one molar equivalent and usually a molar excess of the acid is employed. However when such salts as the sulfate, the hemisuccinate, the hydrogen phosphate or the phosphate are desired, the appropriate and exact chemical equivalents of acid will generally be used. The free base and the acid are usually combined in a co-solvent from which the desired salt precipitates, or can be otherwise isolated by concentration and/or addition of a non-solvent.

15 The amines ($R'NH_2$) and aldehydes ($R'CHO$), when not commercially available or known in the prior art, are available by conventional synthetic methods, as exemplified below. For example the starting aldehydes are generally available as described in WO89/08650, WO89/8651 and WO89/08652 (cited above), and in U.S. Patent 4,725,610; while the amino compounds are most generally available by reduction of the corresponding nitro compounds, as described in that same U.S. Patent 4,725,610.

25 The present compounds of the formulas (I) and (II) are readily adapted to clinical use as hypoglycemic or hypocholesterolemic agents. The activity required for this former clinical use is defined by the test for

-20-

hypoglycemic effect in ob/ob or db/db mice by the following procedure:

Five to eight week old C57BL/6J-ob/ob or
5 C57BL/K_sJ-db/db mice (obtained from Jackson Laboratory,
Bar Harbor, Maine) were housed five per cage under
standard animal care practices. After a one week
acclimation period, the animals were weighed and 25
microliters of blood was collected via an ocular bleed
10 prior to any treatment. The blood sample was
immediately diluted 1:5 with saline containing
2.5 mg/ml sodium fluoride and 2% sodium heparin, and
held on ice for metabolite analysis. Animals were then
dosed daily for five days with drug (5-50 mg/kg), a
15 positive control (50 mg/kg) of ciglitazone; U.S.
Patent 4,467,902; Sohda et al., Chem. Pharm. Bull.,
vol. 32, pp. 4460-4465, 1984), or vehicle. All drugs
were administered in a vehicle consisting of 0.25% w/v
methyl cellulose. On day 5, the animals were weighed
20 again and bled (via the ocular route) for blood
metabolite levels. The freshly collected samples were
centrifuged for two minutes at 10,000 xg at room
temperature. The supernatant was analyzed for glucose,
for example, by the ABA 200 Bichromatic Analyzer™,
25 using the A-gent™ glucose UV reagent system*
(hexokinase method) using 20, 60 and 100 mg/dl
standards. Plasma glucose was then calculated by the
equation,
30 Plasma glucose (mg/dl) = Sample value x 5 x 1.67 =
8.35 x Sample value
where 5 is the dilution factor and 1.67 is the plasma
hematocrit adjustment (assuming the hematocrit is 40%).

-21-

"A registered trademark of Abbott Laboratories, Diagnostics Division, 820 Mission Street, So. Pasadena, CA 91030.

5 *A modification of the method of Richterich and Dauwalder, Schweizerische Medizinische Wochenschrift, 101, 860 (1971).

10 The animals dosed with vehicle maintain substantially unchanged hyperglycemic glucose levels (e.g., 250 mg/dl), while positive control animals have depressed glucose levels (e.g., 130 mg/dl). Test compounds are reported in terms of % glucose normalization. For example, a glucose level which is the same as the positive control is reported as 100%.

15 Studies such as that described below demonstrate that the compounds of formula (I) effect the lowering of serum cholesterol levels in mammals.

20 Female mice (strain C57Br/cd J), obtained from Jackson Laboratories, Bar Harbor, Maine, are used at age 8-12 weeks, following 2-4 weeks acclimation having free access to water and standard laboratory chow. Animals are divided randomly into three groups of 6-7 animals. All three groups are placed on a diet containing 0.75% cholesterol, 31% sucrose, 15.5% starch, 20% casein, 17% cellulose, 4.5% corn oil, 5% coconut oil, 0.25% cholic acid, 4% salts and 2% vitamin; permitted to feed ad lib for 18 days; and dosed daily at 9-11 a.m. for the final 5 days by oral gavage, the control group with 5 ml/kg of vehicle (0.1% aqueous methyl cellulose) and the test groups with the compound under study at doses ranging from 0.1 to 10 mg/kg/day in vehicle. After the fourth day of dosing, the animals are fasted overnight, starting at 5 p.m. The following morning a fifth and final dose of the

25
30

-22-

compound is administered to the test groups and, three hours later, the animals are sacrificed by decapitation. Blood from the body trunk is collected and allowed to clot, and the serum assayed enzymatically, using an
5 Abbott VP automated analyzer, for HDL cholesterol, LDL and VLDL cholesterol, and total cholesterol. Whether judged on the basis LDL + VLDL cholesterol levels, total cholesterol levels or the ratio of LDL + VLDL/HDL,
10 the compounds of this invention generally show favorable result in lowering cholesterol levels.

The present compounds of the formulas (I) and (II) are clinically administered to mammals, including man, via either the oral or the parenteral route. Adminis-
15 tration by the oral route is preferred, being more convenient and avoiding the possible pain and irritation of injection. However, in circumstances where the patient cannot swallow the medication, or absorption following oral administration is impaired,
20 as by disease or other abnormality, it is essential that the drug be administered parenterally. By either route, the dosage is in the range of about 0.10 to about 50 mg/kg body weight of the subject per day, preferably about 0.10 to about 10 mg/kg body weight per
25 day administered singly or as a divided dose. However, the optimum dosage for the individual subject being treated will be determined by the person responsible for treatment, generally smaller doses being administered initially and thereafter increments made
30 to determine the most suitable dosage. This will vary according to the particular compound employed and with the subject being treated.

-23-

The compounds can be used in pharmaceutical preparations containing the compound, or pharmaceutically acceptable acid salt thereof, in combination with a pharmaceutically-acceptable carrier or diluent. Suitable pharmaceutically-acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The active compound will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described above. Thus, for oral administration the compounds can be combined with a suitable solid or liquid carrier or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions may, if desired, contain additional components such as flavorants, sweeteners, excipients and the like. For parenteral administration the compounds can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically-acceptable acid addition salts of the compounds. The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in man.

30

-24-

The present invention is illustrated by the following Examples. However, it should be understood that the invention is not limited to the specific details of these examples. Nomenclature used herein is based on Rigaudy and Klesney, IUPAC Nomenclature of Organic Chemistry, 1979 Ed., Pergammon Press, New York, 1979.

5

10

15

20

25

30

-25-

EXAMPLE 1

3-[4-(2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy)-
phenyl]-2-methylthio-2-propenoic Acid

5 4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]-
benzaldehyde (Takeda U.S. Patent 4,725,610; 0.5 g,
1.6 mmol), rhodanine (0.21 g, 1.6 mmol) and piperidine
(5 drops) were combined in ethanol (10 ml) and heated
to reflux for 2 hours. The mixture was cooled and the
10 precipitate filtered (0.35 g, mp 202.5-203.5°C). A
slurry of this compound (0.25 g, 0.58 mmol) in 15%
sodium hydroxide (5 ml) was heated to gentle reflux for
1 hour, then cooled and treated with a solution of
methyl iodide (0.16 ml, 2.6 mmol) in methanol (5 ml).
15 After 2 hours stirring at room temperature, the mixture
was diluted with ice-water and acidified with 2N hydro-
chloric acid. The precipitate was filtered and
recrystallized from 1:1 ethanol-water (10 ml) (0.11 g,
mp 178.5-182°C).

20 Starting from the same aldehyde and using propyl
iodide as the reagent, 3-[4-(2-(5-methyl-2-phenyl-4-
oxazolyl)ethoxy)phenyl]-2-propylthio-2-propenoic acid
was prepared by the same method (gummy solid).

¹H NMR (CDCl₃, 300 MHz) delta 0.91 (t, J = 7.3Hz,
25 3H), 1.56 (tq, J = 7Hz, 7Hz, 2H), 2.38 (s, 3H),
2.76 (t, J = 7.3Hz, 2H), 3.01 (t, J = 6.6Hz, 2H), 4.29
(t, J = 6.6Hz, 2H), 6.92 (d, J = 8.9Hz, 2H), 7.39-7.44
(m, 3H), 7.94-7.99 (m, 4H), 8.05 (s, 1H).

Starting from 4-[3-(5-methyl-2-phenyl-4-oxazolyl)-
30 propionyl]benzaldehyde (WO89/08650), 3-[4-(3-(5-methyl-
2-phenyl-4-oxazolyl)propionyl)phenyl]-2-methylthio-2-
propenoic acid was prepared by the same method (mp
150-152°C).

-26-

EXAMPLE 23-[4-(2-(5-Methyl-2-phenyl-4-oxazolyl)-
phenyl]-2-(methylthio)propanoic Acid

5 To a solution of 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]aniline (U.S. Patent 4,725,610) (3.7 g, 12.6 mmol) in acetone (50 ml) and methanol (50 ml), cooled to 0°C, was added 48% hydrobromic acid (6.2 ml, 54 mmol), and after 5 minutes a solution of sodium
10 nitrite (1.0 g, 15 mmol) in water (5 ml), dropwise, keeping the temperature below 5°C. After 15 minutes ethyl acrylate (8.6 ml, 79 mmol) was added dropwise, the mixture was warmed to 38°C and cuprous oxide (0.42 g, 2.9 mmol) was added. The solution was stirred 1
15 hour at 40°C, then concentrated, diluted with aqueous ammonia and extracted with ethyl acetate (3 x 30 ml). The combined extracts were washed with water (2 x), brine, dried over magnesium sulfate and concentrated. The product, ethyl alpha-bromo-4-[2-(5-methyl-2-
20 phenyl-4-oxazolyl)ethoxy]benzenepropanoate, was isolated by flash chromatography (hexane/ethyl acetate, 4:1) as a yellow oil (1.17 g).

To a solution of ethyl alpha-bromo-4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzenepropanoate
25 (0.20 g, 0.44 mmol) in dimethylformamide (0.5 ml) was added a solution of sodium thiomethoxide (0.10 g, 1.4 mmol) in water (0.3 ml). The resulting solution was stirred at 80°C for 16 hours. Water was added the mixture was acidified with 2N hydrochloric acid and
30 extracted with ethyl acetate (2 x). The combined extracts were washed with water (5 x) and brine, dried over magnesium sulfate and concentrated to a yellow oil. The product was purified by flash-chromatography

-27-

(hexane/ethyl acetate, 2:1) and obtained as a yellow gum (60 mg).

¹H NMR (CDCl₃, 300 MHz) delta 2.19 (s, 3H), 2.36 (s, 3H), 2.88 (dd, J = 6Hz, 14Hz, 1H), 2.96 (t, J = 7Hz, 2H), 3.16 (dd, J = 9Hz, 14Hz, 1H), 3.41 (dd, J = 6Hz, 9Hz, 1H), 4.13 (t, J = 7Hz, 2H), 6.78 (d, J = 8Hz, 2H), 7.11 (d, J = 8Hz, 2H), 7.39-7.41 (m, 3H), 7.92-7.96 (m, 2H).

EXAMPLE 3

Ethyl 3-[4-(2-(5-Methyl-2-phenyl-4-oxazolyl)-ethoxy)phenyl]-2-(acetylthio)propanoate

To a solution of ethyl alpha-bromo-4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzenepropanoate (0.18 g, 0.38 mmol) and thiolacetic acid (75 µl, 1.05 mmol) in dimethylformamide (2 ml) was added potassium carbonate (0.15 g, 1.05 mmol). After stirring overnight at room temperature, the mixture was poured into water and acidified with 1N hydrochloric acid, then extracted with ethyl acetate (3 x). The combined extracts were washed with water (5 x) and brine, dried over magnesium sulfate and concentrate to a yellow oil (0.11 g).

¹H NMR (CDCl₃, 300 MHz) delta 1.18 (t, J = 7Hz, 3H), 2.31 (s, 3H), 2.37 (s, 3H), 2.91-2.99 (m, 1H), 2.97 (t, J = 7Hz, 2H), 3.13 (dd, J = 8Hz, 14Hz, 1H), 4.10 (q, J = 7Hz, 2H), 4.21 (t, J = 7Hz, 2H), 4.36 (dd, J = 7Hz, 8Hz, 1H), 6.80 (d, J = 8Hz, 2H), 7.09 (d, J = 8Hz, 2H), 7.38-7.42 (m, 3H), 7.94-7.98 (m, 2H).

-28-

EXAMPLE 4

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)-
benzofuran-5-yl]-2-(propylthio)propanoate

- 5 A. alpha-(5-Methyl-2-phenyl-4-oxazolyl)-5-nitro-2-benzofuranmethanol

A solution of 4-bromoacetyl-5-methyl-2-phenyl-oxazole (Takeda U.S. Patent 4,725,610) (53 g, 0.19 mol), 5-nitrosalicylaldehyde (32 g, 0.19 mol) and diisopropylethylamine (66 ml, 0.38 mol) in dimethyl-
10 formamide (250 ml) was heated to 91-94°C for 3 hours. The mixture was cooled, diluted with ethyl acetate (300 ml) and the solid was collected. This solid was washed with chloroform (2 x 100 ml) and dried (56 g, mp 233-234°C). It was then placed in tetrahydrofuran
15 (600 ml) and methanol (300 ml) and the slurry was cooled to 0°C. Sodium borohydride (9.1 g, 0.24 mol) was added portion-wise over 1 hour and the cloudy solution was stirred at 0°C for 2 hours. The bulk of the solvent was removed in vacuo and water (700 ml) was
20 added. The mixture was acidified with 6N hydrochloric acid and stirred for 30 minutes. The yellow-tan solid was collected, washed with water and dried (57 g, mp 166-167°C).

- 25 B. 5-Amino-2-(5-methyl-2-phenyl-4-oxazolyl)-methylbenzofuran

alpha-(5-Methyl-2-phenyl-4-oxazolyl)-5-nitro-2-benzofuranmethanol (57 g, 0.16 mol) was dissolved in trifluoroacetic acid (350 ml), while cooling to 0°C. Triethylsilane (64 ml, 0.40 mol) was added. The
30 solution was stirred 1.5 hours at 0°C and overnight at room temperature. The solution was concentrated to near-dryness and the residue dissolved in ethyl acetate (750 ml). This solution was washed with water. The

-29-

precipitate formed during the wash was collected. The organic solution was washed with saturated sodium bicarbonate, during which more precipitate formed and was collected. The ethyl acetate phase of the filtrate was washed again with saturated sodium bicarbonate, then with brine, dried over sodium sulfate and concentrated. The residue was triturated with isopropyl ether and a solid was obtained. The combined solids obtained hereabove (51 g, 0.15 mol) were placed in a Parr bottle together with platinum oxide (3 g) and ethyl acetate (1.5 l) and hydrogenated at 40 psi for 1.25 hours. The catalyst was filtered through Celite, and after washing the filtering pad with more ethyl acetate, the solvent was removed in vacuo to give a yellow residue which was triturated with isopropyl ether (200 ml). The pale yellow solid was collected (37.1 g, mp 161.5-162.5°C).

C. α -Chloro-2-(5-methyl-2-phenyl-4-oxazolyl)-methyl-5-benzofuranpropanenitrile

To a solution of acrylonitrile (11.2 ml, 0.17 mol) and tert-butyl nitrite (21.4 ml, 0.18 mmol) in acetonitrile (16 ml) was added cupric chloride (19.4 g, 0.14 mol), and 5-amino-2-(5-methyl-2-phenyl-4-oxazolyl)methylbenzofuran (37 g, 0.12 mol) portionwise over 40 minutes. The mixture was stirred for 30 minutes then poured into 20% hydrochloric acid (500 ml) and this solution was extracted with ethyl acetate (2 x 700 ml). The combined extracts were washed with 20% hydrochloric acid (2 x 250 ml), and brine (350 ml), dried over sodium sulfate and concentrated. The thick gum was extracted with boiling hexane (4 x 450 ml), the combined liquid phases were decanted, boiled down to

-30-

ca. 1100 ml and cooled. The solid was collected (6.9 g). The mother liquor was concentrated and the residue was purified by flash-chromatography (hexanes/ethyl acetate, 4:1) to give a yellow solid which was combined with the material obtained from the hot hexane to give 16 g of the title compound as a yellow sticky solid.

D. Ethyl 3-[2-((5-Methyl-2-phenyl-4-oxazolyl)-methyl)benzofuran-5-yl]-2-(propylthio)propanoate

Hydrogen chloride was bubbled into a slurry of 2-(5-methyl-2-phenyl-4-oxazolyl)methyl-alpha-chloro-5-benzofuranpropanenitrile (16.3 g, 43 mmol) in 95% ethanol (600 ml) at 0°C for 30 minutes, after which the mixture was stirred for 3 days at room temperature. The solvent was removed in vacuo and the residue partitioned between saturated sodium bicarbonate (350 ml) and ethyl acetate (500 ml). The aqueous layer was extracted with ethyl acetate (250 ml), the organic phases were combined, washed with brine, dried over sodium sulfate and concentrated. The oily residue was extracted with boiling hexane (2 x 400 ml), the solution was boiled down to 400 ml and cooled. The precipitated solid was collected. The filtrate was boiled down to 250 ml and allowed to cooled overnight and the solid was collected. The two solids were combined (11.5 g, mp 113-115°C).

To a solution of this solid (5 g, 12 mmol) in dimethylformamide (100 ml) was added propyl mercaptan (3.0 gml, 33 mmol), followed by potassium carbonate (4.6 g, 33 mmol). The slurry was stirred at room temperature overnight then poured into water (400 ml), acidified with 6N hydrochloric acid and extracted with

-31-

ethyl acetate (2 x 300 ml). The combined extracts were washed with water (3 x 200 ml) and brine, dried over sodium sulfate and concentrated, leaving a yellow oil (4.3 g).

5 ^1H NMR (CDCl_3 , 300 MHz) delta 0.93 (t, $J = 7.5\text{Hz}$, 3H), 1.15 (t, $J = 7.0\text{Hz}$, 3H), 1.56 (m, 2H), 2.32 (s, 3H), 2.57 (m, 2H), 2.99 (dd, $J = 6.4\text{Hz}$, 13.9Hz, 1H), 3.22 (dd, $J = 9.4\text{Hz}$, 13.6Hz, 1H), 3.48 (dd, $J = 6.4\text{Hz}$, 9.1Hz, 1H), 3.99 (s, 2H), 4.08 (m, 2H), 6.40 (d, $J =$
10 1.1Hz, 1H), 7.03 (dd, $J = 1.6\text{Hz}$, 8.6Hz, 1H), 7.29 (s, 1H), 7.29 (d, $J = 7.8\text{Hz}$, 1H), 7.37-7.42 (m, 3H), 7.96-7.99 (m, 2H).

Using the corresponding mercaptans, the following
15 compounds were prepared by the same procedure:

Ethyl 3-[2-((5-methyl-2-phenyl-4-oxazolyl)methyl)-benzofuran-5-yl]-2-(phenylmethylthio)propanoate (oil)

20 ^1H NMR (CDCl_3 , 300 MHz) delta 1.20 (t, $J = 7\text{Hz}$, 3H), 2.32 (s, 3H), 2.92 (dd, $J = 6\text{Hz}$, 14Hz, 1H), 3.20 (dd, $J = 9\text{Hz}$, 14Hz, 1H), 3.45 (dd, $J = 6\text{Hz}$, 9Hz, 1H), 3.75 (d, $J = 13\text{Hz}$, 1H), 3.80 (d, $J = 13\text{Hz}$, 1H), 4.0 (s, 2H), 4.05 (m, 2H), 6.38 (s, 1H), 6.90 (dd, $J = 2\text{Hz}$, 8Hz), 7.10-7.30 (m, 7H), 7.35-7.45 (m, 3H), 7.92-8.00 (m, 2H).

25 Ethyl 2-ethylthio-3-[2-((5-methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]propanoate (oil)

30 ^1H NMR (CDCl_3 , 300 MHz) delta 1.15 (t, $J = 7.4\text{Hz}$, 3H), 1.20 (t, $J = 7.7\text{Hz}$, 3H), 2.32 (s, 3H), 2.61 (dq, $J = 1.4\text{Hz}$, 7.8Hz, 2H), 3.07 (dd, $J = 6.3\text{Hz}$, 13.8Hz, 1H), 3.23 (dd, $J = 9.6\text{Hz}$, 13.9Hz, 1H), 3.50 (dd, $J = 6.3\text{Hz}$, 9.1Hz, 1H), 3.99 (s, 2H), 4.08 (m, 2H), 6.40 (s, 1H), 7.03 (dd, $J = 1.65\text{Hz}$, 8.6Hz, 1H), 7.29 (s, 1H), 7.29 (d, $J = 8.3\text{Hz}$, 1H), 7.37-7.42 (m, 3H), 7.42-7.99 (m, 2H).

-32-

Ethyl 3-[2-((5-methyl-2-phenyl-4-oxazolyl)methyl)-benzofuran-5-yl]-2-(phenylthio)propanoate (oil)

¹H NMR (CDCl₃, 300 MHz) delta 1.04 (t, J = 7Hz, 3H), 2.32 (s, 3H), 3.08 (dd, J = 6Hz, 14Hz, 1H), 3.22 (dd, J = 9Hz, 14Hz, 1H), 3.88 (dd, J = 6Hz, 9Hz, 1H), 3.95 (m, 2H), 4.00 (s, 3H), 6.38 (s, 1H), 7.00 (d, J = 8Hz, 1H), 7.21-7.30 (m, 6H), 7.35-7.45 (m, 4H), 7.92-7.99 (m, 2H).

Ethyl 3-[2-((5-methyl-2-phenyl-4-oxazolyl)methyl)-benzofuran-5-yl]-2-(octylthio)propanoate (oil)

¹H NMR (CDCl₃, 300 MHz) delta 0.85 (t, J = 6.5Hz, 3H), 1.18 (t, J = 7.0Hz, 3H), 1.22-1.35 (m, 10H), 1.47-1.58 (m, 2H), 2.33 (s, 3H), 2.58 (m, 2H), 2.99 (dd, J = 6.3Hz, 13.8Hz, 1H), 3.22 (dd, J = 9.2Hz, 13.8Hz, 1H), 3.48 (dd, J = 6.3Hz, 9.2Hz, 1H), 3.99 (s, 2H), 4.08 (m, 2H), 6.40 (s, 1H), 7.03 (dd, J = 1.8Hz, 8.5Hz, 1H), 7.28 (s, 1H), 7.29 (d, J = 7.9Hz, 1H), 7.37-7.42 (m, 3H), 7.95-7.99 (m, 2H).

20

EXAMPLE 5

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-(propylthio)propanoic Acid

To a solution of title product of Example 4 (3.8 g, 8.2 mmol) in methanol (100 ml) was added 1N sodium hydroxide (100 ml). The mixture was heated to reflux for 2 hours, cooled, poured onto ice (300 ml) and acidified with 6N hydrochloric acid, then extracted with ethyl acetate (500 ml), during which some precipitated solid was collected. The aqueous phase was extracted again with ethyl acetate (200 ml), the combined extracts were washed with water (300 ml) and brine (300 ml), dried over sodium sulfate and concentrated, leaving a yellow-orange solid. The

-33-

solids were combined and recrystallized from ethyl acetate (150 ml) to give the title compound as an off-white solid (2.5 g, mp 169-170°C).

5 The following compounds were prepared by the same route from the corresponding ethyl esters:

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-propanoic acid (mp 153-154°C)

10 2-Ethylthio-3-[2-((5-methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]propanoic acid (mp 144-145°C)

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-(phenylthio)propanoic acid (mp 160-161°C)

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-(octylthio)propanoic acid (mp 94-96°C)

15

EXAMPLE 6

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-(methylthio)propanoic Acid

20 5-Amino-2-[(5-methyl-2-phenyl-4-oxazolyl)methyl]benzofuran was converted into the title compound according to the procedure of Example 2. Mp 178-179°C.

3-[2-[5-Methyl-2-(3-methylphenyl)-4-oxazolyl]-methyl]benzofuran-5-yl]-2-(methylthio)propanoic acid was prepared by the same procedure using the corresponding starting material. Mp 125-127°C.

25

EXAMPLE 7

Ethyl 2-(Acetylthio)-3-[2-((5-methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]propanoate was prepared from ethyl alpha-bromo-2-(5-methyl-2-phenyl-4-oxazolyl)methyl-5-benzofuranpropanoic acid according to the procedure of Example 3 and obtained as an oil.

¹H NMR (CDCl₃, 300 MHz) delta 1.10 (t, J = 7Hz, 3H), 2.29 (s, 3H), 2.34 (s, 3H), 3.04 (dd, J = 7Hz, 14Hz, 1H), 3.25 (dd, J = 8Hz, 14Hz, 1H), 3.99 (s, 2H),

-34-

4.07 (q, J = 7Hz, 2H), 4.38 (dd, J = 7Hz, 8Hz, 1H),
6.40 (s, 1H), 7.03 (dd, J = 2Hz, 8Hz, 1H), 7.28 (s,
1H), 7.36-7.42 (m, 3H), 7.94-7.98 (m, 2H).

5 Ethyl 2-((Acetylthio)-3-[2-[(5-methyl-2-(3-methylphenyl)-4-oxazolyl)methyl]benzofuran-5-yl]-propanoate was prepared according to the same procedure and obtained as an oil.

10 ¹H NMR (CDCl₃, 300 MHz) delta 1.10 (t, J = 7Hz, 3H), 2.30 (s, 3H), 2.35 (s, 3H), 2.40 (s, 3H), 3.05 (dd, J = 7Hz, 14Hz, 1H), 3.27 (dd, J = 8Hz, 14Hz, 1H), 4.00 (s, 2H), 4.07 (q, J = 7Hz, 2H), 4.39 (dd, J = 7Hz, 8Hz, 1H), 6.40 (s, 1H), 7.04 (dd, J = 2Hz, 8Hz, 1H), 7.18 (d, J = 8Hz, 1H), 7.26-7.30 (m, 3H), 7.75 (d, J =
15 8Hz, 1H), 7.81 (s, 1H).

EXAMPLE 8

Ethyl 3-[2-((5-Methyl-2-phenyl-4-oxazolyl)-methyl)benzofuran-5-yl]-2-(propylsulfinyl)-
propanoate

20 To a solution of title product of Example 4 (0.39 g, 0.85 mmol) in tetrahydrofuran (75 ml) was added at 0°C, 80% *m*-chloroperoxybenzoic acid (0.18 g, 0.85 mmol). After 10 minutes, ethyl vinyl ether (0.5 ml) was added and the solution was diluted with
25 ethyl acetate, washed with water (3 x) and brine, dried over magnesium sulfate and concentrated. Flash-chromatography (hexanes/ethyl acetate, 2:1) gave the expected product as an oil (0.35 g).

30 ¹H NMR (CDCl₃, 300 MHz) delta 1.05 (t, J = 7Hz, 3/2H), 1.09 (t, J = 7Hz, 3/2H), 1.12 (t, J = 7Hz, 3/2H), 1.19 (t, J = 7.1Hz, 3/2H), 1.73-1.94 (m, 2H), 2.34 (s, 3H), 2.56-2.88 (m, 2H), 3.27-3.46 (m, 2H), 3.71-3.78 (m, 1H), 4.01 (s, 2H), 4.05-4.26 (m, 2H),

-35-

6.41 (d, $J = 0.7\text{Hz}$, 1/2H), 6.42 (d, $J = 1.0\text{Hz}$, 1/2H),
7.04 (dd, $J = 1.7\text{Hz}$, 6.9Hz, 1/2H), 7.07 (dd, $J = 1.8\text{Hz}$,
6.7Hz, 1/2H), 7.30-7.33 (m, 2H), 7.36-7.43 (m, 3H),
7.92-8.03 (m, 2H).

5

EXAMPLE 9

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)-
benzofuran-5-yl]-2-(methylsulfonyl)propionic acid

To a solution of title product of Example 5
(0.30 g, 0.74 mmol) in tetrahydrofuran (75 ml) was
added 80% m-chloroperoxybenzoic acid (0.16 g,
0.74 mmol) at 0°C. After 10 minutes, ethyl vinyl ether
(0.5 ml) was added, the solution was diluted with ethyl
acetate, washed with water (3 x) and brine, dried over
magnesium sulfate and concentrated. The product was
isolated by flash-chromatography (hexane/ethyl acetate,
1:1) as a yellow solid (0.11 g, mp 220-203°C).

15

EXAMPLE 10

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)-
benzofuran-5-yl]-2-(propylsulfinyl)propanoic Acid

20

A solution of the title product of Example 8
(0.20 g, 0.42 mmol) in methanol (5 ml) and 1N sodium
hydroxide (5 ml) was stirred at room temperature for 48
hours. It was then poured into water, acidified with
concentrated hydrochloric acid and extracted with ethyl
acetate (3 x). The combined extracts were washed with
water and brine, dried over sodium sulfate and
concentrated to an oil. The product was purified by
flash-chromatography (ethyl acetate/hexane, 10:1) and
obtained as an oily solid (43 mg).

25

30

^1H NMR (CDCl_3 , 300 MHz, 62°C) δ 0.88 (t, $J =$
7Hz, 3/2H), 0.97 (t, $J = 7\text{Hz}$, 3/2H), 1.60 (m, 1H),
1.75 (m, 1H), 2.34 (s, 3/2H), 2.36 (s, 3/2H), 2.55-2.70
(m, 1H), 2.80 (m, 1/2H), 2.91 (m, 1/2H), 3.05 (m,

-36-

1/2H), 3.35 (m, 1H), 3.42-3.51 (m, 1.5H), 3.97 (s, 2/2H), 3.99 (s, 2/2H), 6.34 (s, 1/2H), 6.38 (s, 1/2H), 7.06 (d, J = 7Hz, 1H), 7.20-7.27 (m, 1H), 7.31-7.37 (m, 4H), 7.92-7.95 (m, 2H).

5

EXAMPLE 11

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)-benzofuran-5-yl)-2-(methylthio)-N-(phenyl-sulfonyl)propanamide

10

A mixture of the title product of Example 6 (0.15 g, 0.37 mmol) and thionyl chloride (0.10 ml, 1.4 mmol) was heated on a steam bath for 20 minutes. The mixture was cooled, diluted with benzene and concentrated. A mixture of benzenesulfonamide (0.12 g, 0.74 mmol) and 60% sodium hydride (32 mg, 0.81 mmol) in tetrahydrofuran (5 ml) was heated at reflux for 30 minutes, cooled to 0°C and treated with a solution of this acid chloride in tetrahydrofuran (5 ml). The mixture was heated for 3 hours at reflux and overnight at room temperature. It was then diluted with ethyl acetate, washed with 1N hydrochloric acid, water (2 x) and brine, dried over magnesium sulfate and concentrated. The product was purified by flash-chromatography (3% methanol in dichloromethane) and obtained as an oil.

25

¹H NMR (CDCl₃, 300 MHz) delta 1.90 (s, 3H), 2.36 (s, 3H), 2.92 (dd, J = 8Hz, 14Hz, 1H), 3.14 (dd, J = 8Hz, 14Hz, 1H), 3.38 (t, J = 8Hz, 1H), 3.99 (s, 3H), 6.33 (s, 1H), 6.80 (dd, J = 2Hz, 8Hz, 1H), 7.09 (d, J = 2Hz, 1H), 7.17 (dd, J = 2Hz, 8Hz, 1H), 7.38-7.60 (m, 6H), 7.94-7.98 (m, 4H), 9.00 (br s, 1H).

30

By the same method the following compounds were prepared: 3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)-benzofuran-5-yl)-2-(methylthio)-N-(phenylcarbonyl)-propanamide (mp 62°C).

-37-

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-(methylthio)-N-(4-chlorophenylsulfonyl)propanamide (mp 94-95°C).

5 3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-(methylthio)-N-(4-fluorophenylsulfonyl)propanamide (mp 60-62°C).

3-[2-(5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-(methylthio)-N-(methanesulfonyl)propanamide (mp 63-64°C).

10 3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-(methylthio)-N-[(E)-2-phenylethenylsulfonyl]propanamide (oil).

¹H NMR (CDCl₃, 300 MHz) delta 2.05 (s, 3H), 2.34 (s, 3H), 3.02 (dd, J = 8Hz, 14Hz, 1H), 3.25 (dd, J = 8Hz, 14Hz, 1H), 3.48 (t, J = 8Hz, 1H), 3.98 (s, 2H), 6.30 (s, 1H), 6.95 (d, J = 14Hz, 1H), 6.96 (dd, J = 2Hz, 8Hz, 1H), 7.22 (d, J = 2Hz, 1H), 7.35-7.48 (m, 9H), 7.69 (d, J = 14Hz, 1H), 7.95-8.0 (m, 2H), 9.20 (br s, 1H).

20 3-[2-(5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-(methylthio)-N-(2-naphthylsulfonyl)propanamide (mp 163-166°C).

25 3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-(methylthio)-N-(N,N-diethylaminosulfonyl)propanamide (oil).

30 ¹H NMR (CDCl₃, 300 MHz) delta 1.12 (t, J = 7Hz, 6H), 2.08 (s, 3H), 2.36 (s, 3H), 2.96 (dd, J = 8Hz, 14Hz, 1H), 3.30 (q, J = 7Hz, 4H), 3.40 (t, J = 8Hz, 1H), 4.00 (s, 2H), 6.41 (s, 1H), 7.01 (dd, J = 2Hz, 8Hz, 1H), 7.26 (dd, J = 2Hz, 1H), 7.30 (d, J = 8Hz, 1H), 7.38-7.42 (m, 3H), 7.92-7.96 (m, 2H), 8.72 (s, 1H).

-38-

EXAMPLE 12

Optical Resolution of 3-[2-((5-methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-(propylthio)-
propanoic Acid

5

To a slurry of title product of Example 5 (1.6 g, 3.8 mmol) in benzene (35 ml) was added oxalyl chloride (1.8 ml, 21 mmol). Gas was evolved and the slurry turned into a clear yellow solution within 10 minutes. After two hours the solvent was removed, the residue was dissolved in dioxane (25 ml) and added dropwise to a solution of (S)-(+)-2-phenylglycinol (0.52 g, 3.8 mmol) and triethylamine (0.53 ml) in dioxane (10 ml). After 2 hours, the solvent was removed, water was added to the residue and the mixture was acidified with 6N hydrochloric acid. The solid was collected, dried and recrystallized from ethyl acetate/hexanes then from ethyl acetate to give the less polar isomer (on silica thin-layer chromatography, hexane/ethyl acetate, 1:2) as a pale yellow solid (0.41 g). The combined mother liquors were concentrated and the products separated by flash-chromatography (hexane/ethyl acetate, 1:1). More of the less polar isomer was thus obtained (0.14 g) as well as the more polar isomer (0.39 g).

25

The less polar amide (0.54 g, 0.97 mmol) and p-toluenesulfonic acid (2.8 g, 15 mmol) were placed in water (20 ml) and isopropanol (20 ml) and heated to reflux for three days. The solution was cooled, diluted with water (75 ml) and extracted with ethyl acetate (2 x 75 ml). The combined extracts were washed with water (2 x 75 ml) and brine (75 ml), dried over sodium sulfate and concentrated. The product was purified by flash chromatography (hexanes/ethyl acetate/acetic acid, 16:4:1), then recrystallized from

30

-39-

ethyl acetate (15 ml)/hexane (5 ml). The mother liquor was concentrated to give a white solid (83 mg, $[\alpha]_D = +8.8^\circ$, $c = 1.08$, CDCl_3). This material was subsequently found to be greater than 95% optically pure by conversion back to the amide under neutral conditions (EEDQ) and its NMR spectrum was identical to the one of the racemic material.

In the same manner the more polar amide (0.39 g, 0.71 mmol) was converted into the levorotatory acid (81 mg, $[\alpha]_D = -9.4^\circ$, $c = 1.06$, CDCl_3).

EXAMPLE 13

2-Methoxy-3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)-ethoxy]phenyl]propanoic Acid

A. 4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]-benzeneacetaldehyde

To a slurry of methoxymethyltriphenylphosphonium chloride (11 g, 32 mmol) in tetrahydrofuran (120 ml), cooled to 0°C , was added dropwise a 2.5M solution of n-butyllithium in hexanes (9.8 ml, 25 mmol). The red solution was stirred at 0°C for 30 minutes then a solution of 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-benzaldehyde (Takeda U.S. Patent 4,725,610) (5.0 g, 16 mmol) in tetrahydrofuran (70 ml) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. It was then diluted with water and extracted with ethyl acetate (3 x). The combined extracts were washed with water (2 x) and brine, dried over sodium sulfate and concentrated. The product, a mixture of E and Z 4-[2-[4-(2-methoxyethenyl)phenoxy]-ethyl]-5-methyl-2-phenyloxazole, was isolated by flash-chromatography (hexanes/ethyl acetate, 2:1) as a yellow solid (2.6 g).

-40-

This solid (2.0 g, 6.0 mmol) was dissolved in tetrahydrofuran (100 ml) and 35% perchloric acid (10 ml) was added. The solution was heated to reflux for 1 hour then stirred overnight at room temperature, then diluted with water and extracted with ethyl acetate (2 x). The combined extracts were washed with water and brine, dried over sodium sulfate and concentrated. The residue was purified by flash-chromatography (hexane/ethyl acetate, 4:1) and a yellow solid (0.51 g) was obtained.

B. Ethyl alpha-hydroxy-4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzenepropanoate

To a solution of 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzeneacetaldehyde (0.51 g, 1.6 mmol) and trimethylsilyl cyanide (0.21 ml, 1.6 mmol) in deuteriochloroform (1 ml) was added zinc iodide (1 crystal). The solution was stirred overnight at room temperature, then concentrated to yield the product, 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-alpha-(trimethylsilyloxy)benzenepropanenitrile as an oil.

This oil was dissolved in hydrogen chloride (50 ml), the solution was cooled to 0°C, saturated with hydrogen chloride, and stirred overnight at room temperature, then saturated with hydrogen chloride again and stirred another 24 hours at room temperature. The mixture was poured into water, ethyl acetate was added, then 1N sodium hydroxide so as to get the product in solution. The organic layer was separated, washed with water and brine, dried over sodium sulfate and concentrated to a brown oil which was purified by flash-chromatography (hexanes/ethyl acetate, 3:2). The pure product was obtained as an oil (0.19 g).

-41-

C. 2-Methoxy-4-3-[2-(5-methyl-2-phenyl-4-oxazolyl)-ethoxy]phenylpropanoic acid

A 60% sodium hydride dispersion (40 mg) was washed with hexane and suspended in tetrahydrofuran (10 ml).

5 A solution of ethyl alpha-hydroxy-4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzenepropanoate (0.19 g, 0.48 mmol) in tetrahydrofuran (2 ml) was added and after 10 minutes methyl iodide (0.3 ml, 4.8 mmol) was added. The mixture was stirred at room temperature overnight, then diluted with water, acidified with 2N hydrochloric acid and extracted with ethyl acetate (2 x). The combined extracts were washed with water and brine, dried over sodium sulfate and concentrated. 10 The product was purified by flash-chromatography (hexanes/ethyl acetate/acetic acid, 10:10:1) and obtained as a yellow sticky solid.

¹H NMR (CDCl₃, 300 MHz) delta 2.36 (s, 3H), 2.96 (m, 3H), 3.05 (dd, J = 6Hz, 14Hz, 1H), 3.37 (s, 3H), 3.93 (dd, J = 6Hz, 9Hz, 1H), 4.17 (t, J = 9Hz, 2H), 6.79 (d, J = 8Hz, 1H), 7.10 (d, J = 8Hz, 1H), 7.36-7.40 (m, 3H), 7.92-7.96 (m, 2H).

EXAMPLE 14

2-Methoxy-3[2-((5-methyl-2-phenyl-4-oxazolyl)-methyl)benzofuran-5-yl]propanoic Acid

A. 4-Benzoylamino-1-hexyn-5-one

Acetic anhydride (150 ml) was added to a solution of 2-benzoylamino-4-pentynoic acid (J. Org. Chem. 1983, 48, 3318) (73 g, 0.34 mol) in pyridine (200 ml) and the solution was heated to 90°C for 1 hour, then allowed to cool to 60°C and water (150 ml) was added. The mixture was heated to 85-90°C for 20 minutes, then cooled, diluted with water (300 ml) and extracted with chloroform (2 x 400 ml). The combined extracts were

-42-

washed with water, 1N hydrochloric acid (3 x 500 ml), sodium bicarbonate and brine, and dried over magnesium sulfate. The chloroform solution was decolorized with charcoal, filtered and concentrated. The residue was recrystallized from butyl chloride to yield a tan solid (51 g, mp 101-103°C).

5 B. 5-Methyl-2-phenyl-4-(2-propynyl)oxazole

A solution of 4-benzoylamino-1-hexyn-5-one (30 g, 0.14 mol) in trifluoroacetic anhydride (100 ml) and trifluoroacetic acid (200 ml) was heated to 35-40°C for 6 hours. The solution was concentrated and the residue taken up in ethyl acetate (400 ml). To this solution was added saturated sodium bicarbonate solution (400 ml) followed by solid sodium bicarbonate until the water layer became neutral. The layers were separated, the organic layer was washed with brine, dried over magnesium sulfate and concentrated to give a brown oil (28 g) which was used as such.

10 15 20 C. 2-(5-Methyl-2-phenyl-4-oxazolyl)methyl-5-benzofurancarboxaldehyde

To a slurry of cuprous oxide (12 g, 84 mmol) in pyridine (150 ml) were added a solution of 5-methyl-2-phenyl-4-(2-propynyl)oxazole in pyridine (150 ml) followed by a solution of 4-hydroxy-3-iodobenzaldehyde (35 g, 0.14 mol) in pyridine (100 ml). Bis(triphenylphosphine)palladium (II) chloride (0.50 g, 0.7 mmol) was then added as a solid and the mixture was heated to reflux overnight. The mixture was cooled and concentrated. The residue was taken up in ethyl acetate (250 ml + 3 x 50 ml). The ethyl acetate solution was concentrated and the residue was extracted with hot cyclohexane. The hot solution was filtered and cooled and the solid was collected (29 g).

-43-

D. 5-(2-Methoxyethenyl)-2-[(5-methyl-2-phenyl-4-oxazolyl)methyl]benzofuran

To a slurry of methoxymethylphosphonium chloride (34 g, 0.10 mol) and diisopropylamine (9.9 ml, 75 mmol) in tetrahydrofuran (500 ml) was added a 2.5M n-butyl-lithium solution in hexanes (30 ml, 75 mmol), at -10°C. After 1 hour at 10°C a solution of 2-(5-methyl-2-phenyl-4-oxazolyl)methyl-5-benzofurancarboxaldehyde (16 g, 50 mmol) in tetrahydrofuran (200 ml) was added. The mixture was allowed to warm to room temperature over 2 hours, then poured into water (600 ml) and extracted with ether (3 x). The combined extracts were washed with brine, dried over magnesium sulfate and concentrated. The product was isolated by flash-chromatography (hexanes/ethyl acetate, 4:1) as a solid (14 g).

E. 5-(2,2-Dimethoxyethyl)-2-[(5-methyl-2-phenyl-4-oxazolyl)methyl]benzofuran

A solution of 5-(2-methoxyethenyl)-2-(5-methyl-2-phenyl-4-oxazolyl)methylbenzofuran (0.69 g, 2.0 mmol) and p-toluenesulfonic acid monohydrate (40 mg, 0.21 mmol) in methanol (30 ml) was heated to reflux overnight. The solvent was removed, the residue was taken up in ethyl acetate, the solution was washed with 5% sodium bicarbonate and brine, dried over magnesium sulfate and concentrated to an oil which slowly solidified on standing (0.75 g).

F. 2-Methoxy-3-[2-[(5-methyl-2-phenyl-4-oxazolyl)methyl]benzofuran-5-yl]propanenitrile

To a solution of 5-(2,2-dimethoxyethyl)-2-[(5-methyl-2-phenyl-4-oxazolyl)methyl]benzofuran (0.75 g, 2.0 mmol) in dichloromethane (15 ml) were added trimethylsilyl cyanide (0.80 ml, 6.0 mmol) and boron trifluoride etherate (50 μ l, 0.5 mmol). After 1 hour

-44-

the solution was diluted with dichloromethane, washed with 5% sodium bicarbonate, water and brine, dried over magnesium sulfate and concentrated. The product was purified by flash-chromatography (hexanes/ethyl acetate, 2:1) and isolated as a solid (0.64 g, mp 107-109°C).

G. 2-Methoxy-3-[2-((5-methyl-2-phenyl-4-oxazolyl)-methyl)benzofuran-5-yl]propanoic acid

A mixture of 2-methoxy-3-[2-((5-methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]propanenitrile (0.64 g, 1.7 mmol), ethanol (30 ml) and 6N sodium hydroxide (10 ml) was heated to reflux for 3 hours. Water (30 ml) was added and the solution was acidified with concentrated hydrochloric acid (6 ml), then extracted with ethyl acetate (2 x). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated. The product was recrystallized from ethyl acetate/hexanes and obtained as a white solid (0.47 g, mp 159-160.5°C).

Using the corresponding alcohols, the following compounds were prepared by the same procedure:

2-Ethoxy-3-[2-((5-methyl-2-phenyl-4-oxazolyl)-methyl)benzofuran-5-yl]propanoic acid (mp 164-165.5°C)

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-propoxypropanoic acid (mp 139.5-140.5°C)

3-[2-(5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-(2-propenyloxy)propanoic acid (mp 154-155.5°C)

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-(phenylmethoxy)propanoic acid (mp 123-126°C)

-45-

2-(3-Hydroxypropoxy)-3-[2-((5-methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]propanoic acid (mp 125-127°C)

5 3-[2-(5-Methyl-2-phenyl-4-oxazolyl)methyl]benzofuran-5-yl]-2-(2-propynyloxy)propanoic acid (mp 148-150°C)

From (2H)-3,4-dihydro-2-[(4-(phenylmethoxy)-phenyl)methyl]-6-benzopyrancarboxaldehyde (U.S. Patent 4,798,835), sodium (2H)-3,4-dihydro- α -ethoxy-2-(4-phenylmethoxy)phenylmethyl-6-benzopyranpropanoate was prepared by the same sequence. Mp 61-64°C

EXAMPLE 15

15 2-Methoxy-3-[2-((5-methyl-2-phenyl-4-oxazolyl)-methyl)benzofuran-5-yl]propanamide

A solution of the Step F intermediate, Example 14 (0.24 g, 0.64 mmol) in ethanol (20 ml) was saturated with hydrogen chloride and stirred at room temperature for three days. The solvent was removed, water was added followed by saturated sodium bicarbonate to bring the pH to neutral. This mixture was extracted with ethyl acetate (2 x), the combined extracts were washed with brine and dried over magnesium sulfate overnight. The product was isolated by flash-chromatography (hexanes/ethyl acetate, 1:1) as a white solid (58 mg, mp 164-167°C).

25 2-Ethoxy-3-[2-((5-methyl-2-phenyl-4-oxazolyl)-methyl)benzofuran-5-yl]propanamide was obtained by the same method. Mp 165-168°C.

30

EXAMPLE 16

(E) and (Z)-3-[2-((5-Methyl-2-phenyl-4-oxazolyl)-methyl)benzofuran-5-yl]-2-methoxy-2-propenamide

- 5 A. (E) and (Z)-3-[2-((5-Methyl-2-phenyl-4-oxazolyl)-methyl)benzofuran-5-yl]-2-methoxy-2-propenenitrile

To a slurry of 60% sodium hydride (88 mg, 2.2 mmol) in dimethylformamide (15 ml) was added at 45°C methoxyacetonitrile (0.21 g, 3.0 mmol). This solution was allowed to cool and after 30 minutes was slowly
10 added to a warm (50°C) solution of 2-(5-methyl-2-phenyl-4-oxazolyl)methyl-5-benzofuran carboxaldehyde (Example 14) (0.63 g, 2.0 mmol) in dimethylformamide (10 ml). The mixture was heated to 75-80°C for 1 hour then cooled and poured into a water/ethyl acetate
15 mixture. The layers were separated, the aqueous layer was extracted with ethyl acetate, the combined organic phases were washed with water (3 x), dried over magnesium sulfate and concentrated. Flash-
20 chromatography (hexanes/ethyl acetate, 2.5:1) afforded the two geometrical isomers of the product, the less polar isomer (assigned as Z) as a solid (0.10 g), and the more polar isomer (E) as an oil (0.15 g).

- 25 B. (Z)-3-[2-(5-methyl-2-phenyl-4-oxazolyl)methyl-5-benzofuranyl]-2-methoxy-2-propenamide

A solution of (Z)-3-[2-(5-methyl-2-phenyl-4-oxazolyl)methyl-5-benzofuranyl]-2-methoxy-2-propenenitrile (0.10 g, 0.27 mmol) in methanol (10 ml) and sodium hydroxide (2 ml) was heated to reflux for 3
30 hours then cooled, acidified with 6N hydrochloric acid and extracted with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate and concentrated. The product was purified by

-45-

2-(3-Hydroxypropoxy)-3-[2-((5-methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]propanoic acid (mp 125-127°C)

5 3-[2-(5-Methyl-2-phenyl-4-oxazolyl)methyl]benzofuran-5-yl]-2-(2-propynyloxy)propanoic acid (mp 148-150°C)

10 From (2H)-3,4-dihydro-2-[(4-(phenylmethoxy)-phenyl)methyl]-6-benzopyrancarboxaldehyde (U.S. Patent 4,798,835), sodium (2H)-3,4-dihydro-alpha-ethoxy-2-(4-phenylmethoxy)phenylmethyl-6-benzopyranpropanoate was prepared by the same sequence. Mp 61-64°C

EXAMPLE 15

15 2-Methoxy-3-[2-((5-methyl-2-phenyl-4-oxazolyl)-methyl)benzofuran-5-yl]propanamide

20 A solution of the Step F intermediate, Example 14 (0.24 g, 0.64 mmol) in ethanol (20 ml) was saturated with hydrogen chloride and stirred at room temperature for three days. The solvent was removed, water was added followed by saturated sodium bicarbonate to bring the pH to neutral. This mixture was extracted with ethyl acetate (2 x), the combined extracts were washed with brine and dried over magnesium sulfate overnight. The product was isolated by flash-chromatography
25 (hexanes/ethyl acetate, 1:1) as a white solid (58 mg, mp 164-167°C).

2-Ethoxy-3-[2-((5-methyl-2-phenyl-4-oxazolyl)-methyl)benzofuran-5-yl]propanamide was obtained by the same method. Mp 165-168°C.

30

-46-

EXAMPLE 16

(E) and (Z)-3-[2-((5-Methyl-2-phenyl-4-oxazolyl)-
methyl)benzofuran-5-yl]-2-methoxy-2-propenamide

- 5 A. (E) and (Z)-3-[2-((5-Methyl-2-phenyl-4-oxazolyl)-
methyl)benzofuran-5-yl]-2-methoxy-2-propenenitrile

To a slurry of 60% sodium hydride (88 mg, 2.2
mmol) in dimethylformamide (15 ml) was added at 45°C
methoxyacetonitrile (0.21 g, 3.0 mmol). This solution
was allowed to cool and after 30 minutes was slowly
10 added to a warm (50°C) solution of 2-(5-methyl-2-
phenyl-4-oxazolyl)methyl-5-benzofuran carboxaldehyde
(Example 14) (0.63 g, 2.0 mmol) in dimethylformamide
(10 ml). The mixture was heated to 75-80°C for 1 hour
15 then cooled and poured into a water/ethyl acetate
mixture. The layers were separated, the aqueous layer
was extracted with ethyl acetate, the combined organic
phases were washed with water (3 x), dried over
magnesium sulfate and concentrated. Flash-
20 chromatography (hexanes/ethyl acetate, 2.5:1) afforded
the two geometrical isomers of the product, the less
polar isomer (assigned as Z) as a solid (0.10 g), and
the more polar isomer (E) as an oil (0.15 g).

- 25 B. (Z)-3-[2-(5-methyl-2-phenyl-4-oxazolyl)methyl-5-
benzofuranyl]-2-methoxy-2-propenamide

A solution of (Z)-3-[2-(5-methyl-2-phenyl-4-
oxazolyl)methyl-5-benzofuranyl]-2-methoxy-2-propene-
nitrile (0.10 g, 0.27 mmol) in methanol (10 ml) and
sodium hydroxide (2 ml) was heated to reflux for 3
hours then cooled, acidified with 6N hydrochloric acid
30 and extracted with ethyl acetate. The combined
extracts were washed with brine, dried over magnesium
sulfate and concentrated. The product was purified by

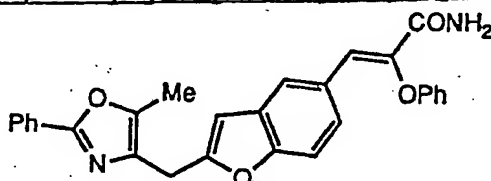
-47-

flash chromatography (ethyl acetate/methanol/acetic acid, 70:1:1) and obtained as a solid (31 mg, m.p. 166-169°C).

The (E) isomer was subjected to the same hydrolysis conditions, and the product isolated as a solid (26 mg, m.p. 160-164°C).

EXAMPLE 17

(E)-3-[2-(5-Methyl-2-phenyl-4-oxazolyl)methyl-5-benzofuranyl]-2-phenoxy-2-propenamide



A. (E)-3-[2-(5-Methyl-2-phenyl-4-oxazolyl)methyl-5-benzofuranyl]-2-phenoxy-2-propenenitrile. To a slurry of 60% sodium hydride (0.10 g, 2.5 mmol) in dimethylformamide (15 ml) was added at 60°C phenoxyacetonitrile (0.21 g, 3.0 mmol). This solution was kept at 60°C for 40 minutes, cooled to room temperature and was slowly added to a warm (80°C) solution of 2-(5-methyl-2-phenyl-4-oxazolyl)methyl-5-benzofurancarboxaldehyde (0.40 g, 2.5 mmol) in dimethylformamide (20 ml). The mixture was heated to 75-80°C for 15 minutes, then cooled and poured into a solution of water (50 ml) and 1N HCl (2.5 ml). The mixture was extracted with ethyl acetate (2X). The combined organic phases were washed with water (3X) and brine, dried over magnesium sulfate and concentrated. Flash chromatography (hexanes/ethyl acetate/triethylamine, 50:50:1) afforded the product as an oil (0.19 g).

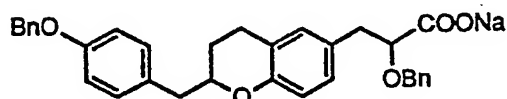
B. (E)-3-[2-(5-Methyl-2-phenyl-4-oxazolyl)methyl]-5-benzofuranyl]-2-phenoxy-2-propenamide. A solution of (E)-3-[2-(5-methyl-2-phenyl-4-oxazolyl)methyl-5-benzofuranyl]-2-phenoxy-2-propenenitrile (0.19 g, 0.44 mmol) in ethanol (10 ml) and sodium hydroxide (2 ml) was heated to reflux for 24 hours, then cooled, poured into a

-48-

mixture of water (50 ml) and ethyl acetate and acidified with 6N hydrochloric acid. The layers were separated, the aqueous layer was extracted with ethyl acetate and the combined organic phases were washed with brine, dried over magnesium sulfate and concentrated. The product was purified by flash chromatography (hexanes/ethyl acetate/acetic acid, 48:8:1) followed by recrystallization from ethyl acetate/hexanes (30 mg, m.p. 171-172.5°C).

EXAMPLE 18

10 Sodium 2-benzyloxy-3-[2-(4-benzyloxybenzyl)-3,4-dihydro-2H-benzopyran-6-yl]propanoate



A. 2-(4-Benzyloxybenzyl)-3,4-dihydro-6-(2-methoxyethenyl)-2H-benzopyran. To a slurry of methoxymethylphosphonium chloride (12.5 g, 37 mmol) and diisopropylamine (9.9 ml, 27.5 mmol) in tetrahydrofuran (40 ml) was added a 2.5 M n-butyllithium solution in hexanes (5.5 ml, 27.5 mmol) at -10°C. After 1 hour at -10°C a slurry of 2-(4-benzyloxy)benzyl-3,4-dihydro-6-formyl-2H-benzopyran (U.S. patent no. 4,798,835) (4.9 g, 18 mmol) in tetrahydrofuran (100 ml) was added. The mixture was allowed to warm to room temperature over 2 hours, then was poured into water (200 ml) and extracted with ethyl acetate (3X). The combined extracts were washed with brine, dried over magnesium sulfate and concentrated. The product was isolated by flash chromatography (hexanes/ethyl acetate, 4:1) as an oil (2.1 g).

B. 2-(4-Benzyloxybenzyl)-6-[2,2-bis(benzyloxy)ethyl]-3,4-dihydro-2H-benzopyran. A solution of 2-[(4-benzyloxy)benzyl]-3,4-dihydro-6-(2-methoxyethenyl)-2H-benzopyran (0.29 g, 0.75 mmol) and benzyl alcohol (1.0 ml, 9.7 mmol) containing Amberlyst 15 ion-exchange resin (100

-49-

mg) was heated to reflux overnight. The resin was filtered and washed with chloroform, the chloroform and the bulk of the benzyl alcohol were removed in vacuo and the residue was purified by flash chromatography
5 (hexanes/ethyl acetate, 4:1) to give the pure product as an oil (0.40 g).

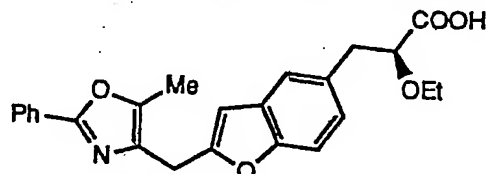
C. 2-Benzyloxy-3-[2-(4-benzyloxybenzyl)-3,4-dihydro-2H-benzopyran-6-yl]propanenitrile. To a mixture of 2-[(4-benzyloxy)benzyl]-6-[2,2-bis(benzyloxy)ethyl]-3,4-dihydro-
10 2H-benzopyran (0.40 g, 0.70 mmol) and trimethylsilyl cyanide (2 ml) was added boron trifluoride etherate (2.06 ml, 0.2 mmol). After 1 hour the reaction was quenched with saturated sodium bicarbonate and the solution was extracted with ethyl acetate (2X). The combined extracts
15 were washed with brine, dried over magnesium sulfate and concentrated. The product was purified by flash chromatography (hexanes/ethyl acetate, 2:1) and isolated as an oily solid (0.23 g).

D. Sodium 2-benzyloxy-3-[-2-(4-benzyloxybenzyl)-3,4-dihydro-2H-benzopyran-6-yl]propanoate. A mixture of 2-benzyloxy-3-[2-(4-benzyloxybenzyl)-3,4-dihydro-2H-benzopyran-6-yl]propanenitrile (0.23 g, 0.47 mmol), ethanol (10 ml) and 6N sodium hydroxide (2 ml) was heated to reflux for 5 hours. Water (50 ml) was added and the
25 solution was acidified with concentrated hydrochloric acid (2 ml), then extracted with ethyl acetate (2X). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated to an oil (0.19 g). The product was dissolved in methanol and treated with
30 sodium methoxide (21 mg). The solvent was removed and the solid dried (7 mg, m.p. 165-169°C).

-50-

EXAMPLE 19

(S)-2-Ethoxy-3-{2-[5-methyl-2-phenyl-4-oxazolyl)methyl]benzofuran-5-yl}propanoic acid



A. (S)-4-Benzyl-3-(ethoxyacetyl)oxazolidin-2-one.

- 5 To a solution of (S)-4-benzyloxazolidin-2-one (4.4 g, 25 mmol) in dry tetrahydrofuran (20 ml), cooled to -78°C , was added n-butyllithium (2.5M solution in hexane, 10 ml, 25 mmol) dropwise. Another 20 ml of tetrahydrofuran was added to facilitate stirring. A solution of ethoxyacetyl
- 10 chloride (3.0 g, 25 mmol) in tetrahydrofuran (5 ml) was added and the mixture was stirred at -78°C for 30 minutes, then warmed to room temperature, poured into water and extracted with ethyl acetate (3X). The combined extracts were washed with water and brine, dried over sodium
- 15 sulfate and concentrated to a yellow oil (4.3 g, $[\alpha]_D = +56.7^{\circ}$).

- B. 5-((1R, 2S)-1-hydroxy-2-ethoxy-3-[(S)-4-benzyl-2-oxo-3-oxazolidinyl]-3-oxopropyl)-2-[(5-methyl-2-phenyl-4-oxazolyl)methyl]benzofuran. To a solution of (S)-4-
- 20 benzyl-3-(ethoxyacetyl)oxazolidin-2-one (1.0 g, 3.8 mmol) in dichloromethane (10 ml), cooled to 0°C , was added freshly distilled dibutylboron triflate (1.1 ml, 4.6 mmol) dropwise, followed by triethylamine (0.69 ml, 4.9 mmol). After 5 minutes the solution was cooled to -78°C and a
- 25 precooled solution of 2-(5-methyl-2-phenyl-4-oxazolyl)methyl-5-benzofurancarboxaldehyde (1.33 g, 4.2 mmol) in dichloromethane (5 ml) was added. After 20 minutes the mixture was warmed to 0°C and stirred at that temperature for 1 hour then quenched with a solution of pH 7 buffer
- 30 (10 ml) in methanol (30 ml), followed by a solution of 30% hydrogen peroxide (10 ml) in methanol (30 ml), and stirred at 0°C for 1 hour. The mixture was then diluted with

-51-

water and extracted with ethyl acetate (3X). The combined extracts were washed with brine, dried over sodium sulfate and concentrated. The product was purified by flash chromatography (hexanes/ethyl acetate, 1:1) and obtained
5 as a yellow solid (1.16 g, m.p. 66°C).

C. 5-((S)-2-Ethoxy-3-[(S)-4-benzyl-2-oxo-3-oxazolidinyl]-3-oxopropyl)-2-[(5-methyl-2-phenyl-4-oxazolyl)methyl]benzofuran. To a solution of 5-((1R, 2S)-1-hydroxy-2-ethoxy-3-[(S)-4-benzyl-2-oxo-3-oxazolidinyl]-3-oxopropyl)-2-[(5-methyl-2-phenyl-4-oxazolyl)methyl]benzopyran (1.0 g, 1.72 mmol) in
10 trifluoroacetic acid (20 ml) was added triethylsilane (3.0 ml, 19 mmol). The solution was stirred for 4 days at room temperature then diluted with ethyl acetate, washed with
15 water and saturated sodium bicarbonate solution (3X), dried over sodium sulfate and concentrated. The product was isolated by flash chromatography (hexanes/ethyl acetate, 5:1) as a pale yellow solid (0.44 g).

D. (S)-2-Ethoxy-3-{2-[(5-methyl-2-phenyl-4-oxazolyl)methyl]benzofuran-5-yl}propanoic acid. 5-((S)-2-Ethoxy-3-[(S)-4-benzyl-2-oxo-3-oxazolidinyl]-3-oxopropyl)-2-[(5-methyl-2-phenyl-4-oxazolyl)methyl]benzofuran (0.15 g, 0.26 mmol) was dissolved in tetrahydrofuran (5 ml). The
20 solution was cooled to 0°C and 0.5N lithium hydroxide (1.1 ml, 0.52 mmol) was added. After 15 minutes the bulk of the ethanol was removed, the residue was acidified with 1N HCl, diluted with water and extracted with ethyl acetate (3X). The combined extracts were washed with brine, dried
25 over sodium sulfate and concentrated. The product was
30 purified by flash chromatography (hexanes/ethyl acetate/acetic acid, 10:10:1) then recrystallized from hexanes/ethyl acetate and obtained as a white solid (48 mg, m.p. 129°C, $[\alpha]_D = -12.5^\circ$ (c 0.99, CDCl_3)).

-52-

Using the appropriate reagents, the following compounds were prepared by the same procedure.

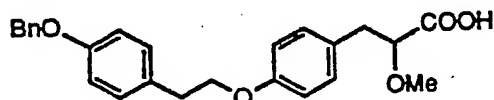
(R)-2-Ethoxy-3-{2-[(5-methyl-2-phenyl-4-oxazolyl)methyl]benzofuran-5-yl}propanoic acid (m.p. 129°C, $[\alpha]_D = +9.3^\circ$ (c 0.65, CDCl_3)).

(R)-3-{2-[(5-Methyl-2-phenyl-4-oxazolyl)methyl]benzofuran-5-yl}-2-phenoxypropanoic acid (m.p. 174-175°C, $[\alpha]_D = -13.1^\circ$ (c 0.50, CDCl_3)).

(S)-3-{2-[(5-Methyl-2-phenyl-4-oxazolyl)methyl]benzofuran-5-yl}-2-phenoxypropanoic acid (m.p. 165°C, $[\alpha]_D = +8.1^\circ$ (c 0.07, CDCl_3)).

EXAMPLE 20

3-[[4-(4-Benzyloxyphenyl)ethoxy]phenyl]-2-methoxypropanoic acid



15 A. 1-Benzyloxy-4-(2-hydroxyethyl)benzene. To a solution of 4-hydroxyphenethyl alcohol (33 g, 0.24 mol) in dry dimethylformamide (200 ml), cooled to 0°C, was added potassium *tert*-butoxide (29 g, 0.26 mol) by portions. After 10 minutes, benzyl bromide (41 g, 0.28 mol) was
20 added slowly. The reaction mixture was stirred for 15 minutes at 0°C, then for 3 hours at room temperature and was quenched with water (200 ml). The precipitate was collected, dried and recrystallized from isopropyl ether/hexanes (34 g).

25 B. 4-[(4-Benzyloxyphenyl)ethoxy]benzonitrile. To a suspension of sodium hydride (60%, 2.2 g, 55 mmol) in dry tetrahydrofuran (250 ml) was added a solution of 1-benzyloxy-4-(2-hydroxyethyl)benzene (11.4 g, 50 mmol) in

-53-

tetrahydrofuran (50 ml). The reaction was heated to 40°C for 1 hour. 4-Fluorobenzonitrile (6.7 g, 55 mmol) was added and the mixture was heated to reflux for 5 hours, cooled and neutralized with concentrated HCl. The
5 precipitate was filtered, the filtrate was concentrated to dryness and the resulting solid was recrystallized from ethanol (12 g).

C. 4-[(4-Benzyloxyphenyl)ethoxy]benzaldehyde. 4-
[(4-Benzyloxyphenyl)ethoxy]benzonitrile (4.9 g, 15 mmol)
10 was dissolved in toluene (300 ml) and treated with a 1.5M toluene solution of diisobutylaluminum hydride (10 ml, 15 mmol). The reaction mixture was stirred overnight then quenched with a saturated sodium potassium tartrate solution (100 ml). The organic layer was washed with 5%
15 sulfuric acid (50 ml), saturated sodium bicarbonate (100 ml) and brine, dried over magnesium sulfate and concentrated to dryness. The product was purified by flash chromatography (hexanes/ethyl acetate, 5:1) and obtained as an oil (4.0 g).

20 This aldehyde was converted into 2-methoxy-3-[[4-(4-benzyloxyphenyl)ethoxy]phenyl]propanoic acid (m.p. 65-69°C) by the sequence described in Example 18.

Using the appropriate reagents, the following compounds were prepared by the same procedure.

25 3-[[4-(4-Benzyloxyphenyl)ethoxy]phenyl]-2-ethoxypropanoic acid (m.p. 62- 63.5°C).

3-[[4-(4-(3-Fluorobenzyloxy)phenyl)ethoxy]phenyl]-2-methoxypropanoic acid (m.p. 58-62°C).

2-Ethoxy-3-[[4-(4-(3-fluorobenzyloxy)phenyl)ethoxy]
30 phenyl]propanoic acid (m.p. 54.5-57.5°C).

-54-

2-Benzyloxy-3-([4-(4-benzyloxyphenyl)ethoxy]phenyl)propanoic acid (m.p. 85-86°C).

3-[3-(5-Ethyl-2-pyridyl)propoxy]phenyl-2-methoxypropanoic acid (m.p. 81-82°C).

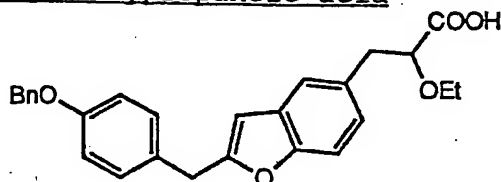
5 2-Ethoxy-3-[3-(5-ethyl-2-pyridyl)propoxy]phenylpropanoic acid (m.p. 80-81°C).

3-[3-(5-Ethyl-2-pyridyl)propoxy]phenyl-2-propoxypropanoic acid (m.p. 89-90°C).

2-Ethoxy-3-(4-[3-(5-methyl-2-phenyl-4-oxazolyl)propanoyl]phenyl)propanoic acid (oil). ¹H NMR (250 MHz, CDCl₃) δ 1.11 (t, J=6.9 Hz, 3H), 2.37 (s, 3H), 2.92 (t, J=7.1 Hz, 2H), 2.94-3.09 (m, 2H), 3.13 (dd, J=13.9 Hz, 4.04 Hz, 1H), 3.35 (t, J=7.1 Hz, 3H), 3.60 (m, 1H), 3.61 (dd, J=9.1 Hz, 7.0 Hz, 1H), 7.32 (d, J=8.3 Hz, 2H),
 15 7.36-7.44 (m, 3H), 7.89 (d, J=8.3 Hz, 2H), 7.94-7.98 (m, 2H), 8.95 (br s, 1H).

EXAMPLE 21

3-[2-(4-Benzyloxybenzyl)benzo-furan-5-yl]-2-ethoxypropanoic acid



20 A. 5-Bromo-2-(4-benzyloxybenzoyl)benzofuran. 5-Bromosalicylaldehyde (2.9 g, 14.5 mmol), cesium carbonate (2.5 g, 7.7 mmol) and acetonitrile (40 ml) were combined and heated to reflux for 30 minutes. The mixture was cooled to 0°C and a solution of 4'-benzyloxy-2-bromoacetophenone (J. Het. Chem., 2, 310 (1965)) (4.7 g, 15 mmol) in
 25 acetonitrile (20 ml) was added. The cooling bath was removed, the mixture stirred at room temperature for 2.5 hours and the precipitate collected (4.5 g).

-55-

B. 5-Bromo-2-(4-benzyloxybenzyl)benzofuran. 5-Bromo-2-(4-benzyloxybenzoyl)benzofuran (9.0 g, 22 mmol), sodium cyanoborohydride (10.4 g, 0.17 mol), zinc iodide (10.5 g, 0.35 mol) and 1,2-dichloroethane (350 ml) were combined and heated to reflux for 6 hours. The mixture was cooled, quenched with saturated ammonium chloride (500 ml), acidified with concentrated HCl and stirred for 30 minutes. The layers were separated, the aqueous layer was extracted with dichloromethane (400 ml) and the combined organic layers were washed with water and brine, dried over magnesium sulfate and concentrated, leaving a white solid (8.5 g).

C. 2-(4-Benzyloxybenzyl)-5-cyanobenzofuran. A mixture of 5-bromo-2-(4-benzyloxybenzyl)benzofuran (4.4 g, 11 mmol), copper cyanide (1.50 g, 17 mmol) and bis(tri-phenylphosphine) palladium (II) chloride (0.79 g, 1.1 mmol) in DMF (40 ml) was heated to reflux overnight. The mixture was cooled, ethyl acetate (200 ml) and concentrated ammonium hydroxide (100 ml) were added. The organic layer was washed with water (3X) and brine, dried over magnesium sulfate and concentrated. The product was purified by flash chromatography (hexanes/ethyl acetate, 5:1) and obtained as a solid (2.6 g, m.p. 131.5-132.5°C). This compound was transformed into the corresponding aldehyde as in Example 20 and into 3-[2-(4-benzyloxybenzyl)benzofuran-5-yl]-2-ethoxypropanoic acid (m.p. 91-94°C) by the sequence described in Example 18.

The following compounds were prepared by the same sequence from the appropriate starting materials and reagents.

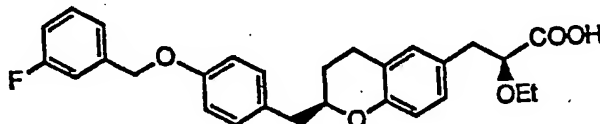
3-[2-(4-Benzyloxybenzyl)benzofuran-5-yl]-2-methoxypropanoic acid (m.p. 98-100°C).

-56-

2-Benzyloxy-3-[2-(4-benzyloxybenzyl)benzofuran-5-yl]propanoic acid (m.p. 115-116.5°C).

EXAMPLE 22

5 (S)-3,4-Dihydro-2-ethoxy-3-[(R)-2-[4-(3-fluorobenzyloxy)benzyl]-2H-benzopyran-6-yl]propanoic acid



A. (R)-(-)-3,4-Dihydro-2-(4-methoxybenzyl)-2H-benzopyran. (R)-(-)-3,4-Dihydro-2-trifluoromethanesulfonyloxymethyl-2H-benzopyran (23.0 g, 78 mmol) and copper (I) bromide dimethyl sulfide complex (2.8 g, 13 mmol) were dissolved in tetrahydrofuran (400 ml) under a nitrogen atmosphere and cooled to -10°C. 4-Anisylmagnesium bromide (215 ml of a 1M solution in tetrahydrofuran, 0.215 mol) was added dropwise over 30 minutes, keeping the temperature below -5°C. The solution was stirred for 3 hours at 0°C and then slowly poured into a mixture of water (800 ml) containing ammonium chloride (96 g, 1.8 mol) and methylene chloride (400 ml). The layers were separated and the aqueous portion was extracted with methylene chloride (400 ml). The combined organics were washed with 10% ammonium chloride (2 X 400 ml), water (250 ml), and brine (250 ml). The methylene chloride layer was dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified on silica gel using hexanes/methylene chloride (1:1) as eluent to afford 18.5 g (92% yield) of the title product as an oil. $[\alpha]_D -99.2^\circ$ (c 1.7, MeOH); ¹H NMR (300 MHz, CDCl₃) δ 1.6-1.7 (m, 1H), 1.9-2.0 (m, 1H), 2.7-2.8 (m, 3H), 3.1 (dd, 1H), 3.8 (s, 3H), 4.1 (m, 1H), 6.8 (m, 3H), 7.0 (m, 2H), 7.2 (m, 2H).

B. (R)-(-)-3,4-Dihydro-2-(4-hydroxybenzyl)-2H-benzopyran. (R)-(-)-3,4-Dihydro-2-(4-methoxybenzyl)-2H-benzopyran (812 mg, 3.2 mmol), and lithium iodide (750 mg, 5.6 mmol) were dissolved in 2,4,6-collidine (2 ml) and heated

-57-

to reflux for 24 hours. The reaction mixture was cooled, diluted with ethyl acetate (20 ml) and 10% HCl (20 ml), and stirred for 10 minutes. The layers were separated and the aqueous portion was extracted with ethyl acetate (50 ml). The combined organics were washed with water (20 ml), brine (20 ml), and were dried (MgSO₄). The solvent was removed in vacuo and the residue purified on silica gel using hexanes/ethyl acetate (3:1) as eluent to afford 730 mg of a colorless oil which crystallized upon standing, m.p. 60-62°C; $[\alpha]_D -110.2^\circ$ (c 1.0, MeOH); ¹H NMR (300 MHz, CDCl₃) δ 1.7 (m, 1H), 2.0 (m, 1H), 2.7-2.8 (m, 3H), 3.1 (dd, 1H), 4.2 (m, 1H), 6.8 (m, 3H), 7.0-7.2 (m, 4H).

C. (R)-(-)-2-(4-Acetoxybenzyl)-3,4-dihydro-2H-benzopyran. (R)-(-)-3,4-Dihydro-2-(4-hydroxybenzyl)-2H-benzopyran (5.0 g, 20 mmol), 4-dimethylaminopyridine (240 mg, 2 mmol), triethylamine (2.6 g, 25 mmol) and acetic anhydride (2.9 g, 28 mmol) were dissolved in methylene chloride (75 ml) and stirred at room temperature for 2 hours under a nitrogen atmosphere. The solvent was removed in vacuo and the residue purified on silica gel using hexanes/ethyl acetate (3:1) as eluent to afford an oil which was crystallized from hexanes to yield 4.0 g of the title product, m.p. 64-65°C; $[\alpha]_D -98.9^\circ$ (c 1.3, MeOH); ¹H NMR (300 MHz, CDCl₃) δ 1.7 (m, 1H), 1.9 (m, 1H), 2.3 (s, 3H), 2.7 (m, 2H), 2.8 (dd, 1H), 3.1 (m, 1H), 4.2 (m, 1H), 6.8 (m, 2H), 7.0 (m, 3H), 7.2 (m, 2H).

D. (R)-(-)-2-(4-Acetoxybenzyl)-3,4-dihydro-6-formyl-2H-benzopyran. (R)-(-)-2-(4-Acetoxybenzyl)-3,4-dihydro-2H-benzopyran (16.6 g, 59 mmol), N-methylformanilide (23.9 g, 0.177 mol), and phosphorus oxychloride (18.0 g, 0.118 mol) were heated to 90°C for 3 hours under a nitrogen atmosphere. The reaction mixture was cooled and poured into ice water (250 ml). The aqueous solution was extracted with ethyl acetate (2 X 500 ml) and the

-58-

combined organics were washed with saturated NaHCO_3 (250 ml), water (250 ml), brine (250 ml), and dried (MgSO_4). The solvent was removed in vacuo and the residue purified on silica gel using hexanes/ethyl acetate (3:1) as eluent to afford 15.7 g (86% yield) of the 6-formyl derivative, ^1H NMR (300 MHz CDCl_3) δ 1.8 (m, 1H), 2.1 (m, 1H), 2.3 (s, 3H), 2.8 (m, 2H), 2.9 (m, 1H), 3.1 (m, 1H), 4.3 (m, 1H), 6.9 (d, 1H), 7.0 (d, 2H), 7.3 (d, 2H), 7.6 (m, 2H), 9.8 (s, 1H).

10 E. (R)-(-)-3,4-Dihydro-6-formyl-2-(4-hydroxybenzyl)-2H-benzopyran. (R)-(-)-2-(4-Acetoxybenzyl)-3,4-dihydro-6-formyl-2H-benzopyran (15.7 g, 51 mmol) was dissolved in a mixture of methanol (200 ml), tetrahydrofuran (200 ml) and 2M NaOH (200 ml) and stirred at room temperature for 2
15 hours. The reaction mixture was concentrated in vacuo, diluted with water (100 ml) and acidified with 10% HCl (250 ml). The aqueous solution was extracted with ethyl acetate (2 X 500 ml) and the combined organics were washed with water (250 ml), brine (250 ml), and dried (MgSO_4).
20 The solvent was removed in vacuo and the residue was crystallized from hexanes/ethyl acetate (3:1) to afford 10.1 g of the title compound, m.p. 134-135°C; $[\alpha]_D -155.2^\circ$ (c 1.0, MeOH); ^1H NMR (300 MHz CDCl_3) δ 1.6 (m, 1H), 1.9 (m, 1H), 2.8 (m, 3H), 3.0 (dd, 1H), 4.2 (m, 1H), 5.1 (br
25 s, 1H, OH), 6.7 (d, 2H), 6.8 (d, 1H), 7.0 (d, 2H), 7.5 (m, 2H), 9.7 (s, 1H).

F. (R)-2-[4-(3-Fluorobenzyloxy)benzyl]-3,4-dihydro-6-formyl-2H-benzopyran. To a solution of (R)-3,4-dihydro-6-formyl-2-(4-hydroxybenzyl)-2H-benzopyran (1.8 g, 6.7
30 mmol) in DMF (10 ml) at 0°C was added potassium tert-butoxide (0.83 g, 7.4 mmol). After 30 minutes *m*-fluorobenzyl bromide (0.91 ml, 7.4 mmol) was added and the resulting slurry was warmed to room temperature and stirred for 2 hours. Water was added and the precipitate
35 was collected, washed with water and air dried (2.5 g).

-59-

G. (R)-6-((1R, 2S)-1-Hydroxy-2-ethoxy-3-[(S)-4-benzyl-2-oxo-3-oxazolidinyl]-3-oxopropyl)-2-[4-(3-fluorobenzyloxy)benzyl]-2H-benzopyran. Trifluoromethanesulfonic acid (0.64 ml, 7.2 mmol) was added to a 1M solution of triethylborane in toluene (7.2 ml, 7.2 mmol) and the mixture was heated to 40°C for 1 hour then cooled to 0°C. A solution of (S)-4-benzyl-3-(ethoxyacetyl)oxazolidin-2-one (Example 19) (0.64 g, 3.6 mmol) in dichloromethane (5 ml) was added, followed by diisopropylethylamine (1.33 ml, 7.6 mmol). After 30 minutes the solution was cooled to -78°C and a solution of (R)-2-[4-(3-fluorobenzyloxy)benzyl]-3,4-dihydro-6-formyl-2H-benzopyran (1.0 g, 3.6 mmol) in dichloromethane (15 ml) was added. The mixture was stirred at -78°C for 2 hours then 30 minutes at 0°C and quenched with pH 7 buffer (5 ml). The mixture was diluted with ether, the organic layer was washed with water and brine, dried over magnesium sulfate and concentrated. The product was isolated by flash chromatography (hexanes/ethyl acetate, 3:2) as an oil (85 mg).

H. (R)-6-[(S)-2-Ethoxy-3-[(S)-4-benzyl-2-oxo-3-oxazolidinyl]-3-oxopropyl]-2-[4-(3-fluorobenzyloxy)benzyl]-2H-benzopyran. (R)-6-((1R, 2S)-1-Hydroxy-2-ethoxy-3-[(S)-4-benzyl-2-oxo-3-oxazolidinyl]-3-oxopropyl)-2-[4-(3-fluorobenzyloxy)benzyl]-2H-benzopyran (80 mg, 0.13 mmol) was dissolved in trifluoroacetic acid (2 ml) and triethylsilane (0.20 ml) was added. After 30 minutes the solution was diluted with ether, washed with water (2X) and saturated sodium bicarbonate (2X), dried over magnesium sulfate and concentrated. The product was purified by flash chromatography (hexanes/ethyl acetate, 2:1) and obtained as an oil (39 mg).

I. (S)-2-Ethoxy-3-[(2R)-2-[4-(3-fluorobenzyloxy)benzyl]-3,4-dihydro-2H-benzopyran-6-yl]propanoic acid. (R)-6-[(S)-2-Ethoxy-3-[(S)-4-benzyl-2-oxo-3-oxazolidinyl]-

-60-

3-oxopropyl)-2-[4-(3-fluorobenzyloxy)benzyl]-2H-benzopyran (39 mg, 63 mmol) was dissolved in tetrahydrofuran (1.5 ml) at 0°C and treated with 0.5N lithium hydroxide (1 ml). The reaction mixture was warmed to room temperature and stirred for 1 hour, then acidified with 1N hydrochloric acid and extracted with ethyl acetate (3X). The combined extracts were washed with water and brine, dried over magnesium sulfate and concentrated. The product was purified by flash chromatography (hexanes/ethyl acetate/acetic acid, 15:5:1) and isolated as an oil (30 mg). ¹H NMR (300 MHz, CDCl₃) δ 1.16 (t, J=6.9 Hz, 3H), 1.67 (m, 1H), 1.93 (m, 1H), 2.68-2.72 (m, 2H), 2.79 (dd, J=13.8 Hz, 6.9 Hz, 1H), 2.88 (dd, J=14.4 Hz, 7.7 Hz, 1H), 3.00 (dd, J=12.2 Hz, 4.3 Hz, 1H), 3.05 (dd, J=13.4 Hz, 7.6 Hz, 1H), 3.43 (m, 1H), 3.58 (m, 1H), 4.01 (dd, J=7.5 Hz, 4.2 Hz, 1H), 4.12 (m, 1H), 5.03 (s, 2H), 6.71 (d, J=8.2 Hz, 1H), 6.88-7.02 (m, 3H), 6.89 (d, J=8.5 Hz, 2H), 7.12-7.18 (m, 2H), 7.17 (d, J=8.6 Hz, 2H), 7.32 (m, 1H).

The following compounds were prepared from the corresponding aldehydes (Example 20) by the same sequence.

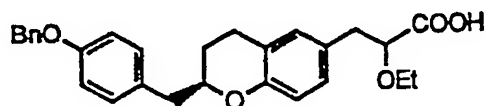
(S) Sodium 2-ethoxy-3-([4-(4-(3-fluorobenzyloxy)phenyl)ethoxy]phenyl)propanoate (m.p. 195-200°C).

(R) Sodium 2-ethoxy-3-([4-(4-(3-fluorobenzyloxy)phenyl)ethoxy]phenyl)propanoate (m.p. 200-205°C).

25

EXAMPLE 23

Sodium 3,4-dihydro-2-ethoxy-3-[(R)-2-(4-benzyloxybenzyl)-2H-benzopyran-6-yl]propanoate



(R)-(-)-3,4-Dihydro-6-formyl-2-(4-hydroxybenzyl)-2H-benzopyran (Example 22) was transformed into the title

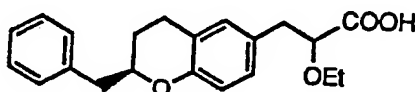
-61-

compound by a sequence analogous to the one described in Example 18, m.p. 160-170°C (dec.).

Using the corresponding reagent, 3,4-dihydro-2-ethoxy-3-[(R)-2-[4-(5-ethyl-2-pyridyl)methoxy]-2H-benzopyran-6-yl]propanoate was prepared by the same method, m.p. 108-109°C.

EXAMPLE 24

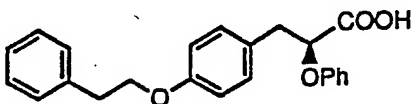
Sodium 3,4-dihydro-2-ethoxy-3-[(R)-2-benzyl-2H-benzopyran-6-yl]propanoate



(R)-(-)-3,4-Dihydro-6-formyl-2-benzyl-2H-benzopyran was prepared from (R)-(-)-3,4-dihydro-2-trifluoromethanesulfonyloxymethyl-2H-benzopyran and phenylmagnesium bromide as described in Example 22 and converted to the title compound as in Example 18 (foam). ¹H NMR (300 MHz, CDCl₃) δ 1.2 (t, 3H), 1.7 (m, 1H), 2.0 (m, 1H), 2.8-3.1 (m, 6H), 3.4 (m, 1H), 3.6 (m, 1H), 4.0 (dd, 1H), 4.1 (m, 1H), 6.7 (d, 2H), 6.9 (s, 1H), 6.95 (dd, 1H), 7.2 (m, 5H).

EXAMPLE 25

2-Phenoxy-3-[4-(2-phenyl)ethoxyphenyl]propanoic acid



A. (S)-4-Benzyl-3-[(1S), (2R)-2-(4-benzyloxyphenyl)-2-hydroxy-1-phenoxyethyl]-2-oxazolidinone. Trifluoromethanesulfonic acid (5.0 ml, 56 mmol) was added to a solution of triethylborane in hexanes (56 ml of a 1M solution, 56 mmol). After the bubbling stopped, the solution was heated to 40°C for 1 hour then cooled to 0°C, a solution of (S)-4-benzyl-3-(phenoxyacetyl)oxazolidin-2-

-62-

one (prepared as in Example 19) (5.0 g, 28 mmol) in dichloromethane (90 ml) was added followed by diisopropylethylamine (12.3 ml, 71 mmol) dropwise. After 30 minutes the solution was cooled to -78°C and treated with a
5 solution of 4-benzyloxybenzaldehyde (6.0 g, 28 mmol) in dichloromethane (80 ml). After 2 hours at -78°C, the solution was warmed to 0°C, stirred for 30 minutes and quenched with pH 7 buffer. The layers were separated, the aqueous portion was extracted with dichloromethane, the
10 combined extracts were washed with water and brine, dried over magnesium sulfate and concentrated. The product was isolated by flash chromatography (hexanes/ethyl acetate, 1:1) as an oil (6.5 g).

B. (S)-4-Benzyl-3-[(1S)-2-(4-benzyloxyphenyl)-1-phenoxyethyl]-2-oxazolidinone. Triethylsilane (20 ml, 125
15 mmol) was added dropwise to a solution of (S)-4-benzyl-3-[(1S), (2R)-2-(4-benzyloxyphenyl)-2-hydroxy-1-phenoxyethyl]-2-oxazolidinone (6.5 g, 12.4 mmol). The solution was stirred for 1 hour then was diluted with ether, washed
20 with water (2X), saturated sodium bicarbonate (2X, carefully), dried over magnesium sulfate and concentrated. The product was isolated by flash chromatography (hexanes/ethyl acetate, 4:1) as an oil (1.8 g).

C. (S)-4-Benzyl-3-[(1S)-2-(4-hydroxyphenyl)-1-phenoxyethyl]-2-oxazolidinone. A solution of (S)-4-benzyl-3-[(1S)-2-(4-benzyloxyphenyl)-1-phenoxyethyl]-2-oxazolidinone (1.8 g) in ethyl acetate (50 ml) containing
25 10% palladium on carbon (1.8 g) was hydrogenated at 40 psi overnight. The catalyst was filtered, the solution concentrated and the product purified by flash
30 chromatography (hexanes/ethyl acetate, 3:2) as an oil (0.81 g).

D. (S)-4-Benzyl-3-[(1S)-2-[4-(2-phenylethoxy)phenyl]-1-phenoxyethyl]-2-oxazolidinone. To a solution of

-63-

(S)-4-benzyl-3-[(1S)-2-(4-hydroxyphenyl)-1-phenoxyethyl]-2-oxazolidinone (0.25 g, 0.60 mmol), phenethyl alcohol (80 ml, 0.66 mmol) and triphenylphosphine (0.17 g, 0.66 mmol) in tetrahydrofuran (5 ml) was added diisopropylazodicarboxylate (0.13 ml, 0.66 mmol). The mixture was stirred overnight in the dark, then concentrated. The product was isolated by flash chromatography (hexanes/ethyl acetate, 3:1) as a white solid (0.28 g).

E. 2-Phenoxy-3-[4-(2-phenyl)ethoxyphenyl]propanoic acid. A solution of (S)-4-benzyl-3-[(1S)-2-[4-(2-phenylethoxy)phenyl]-1-phenoxyethyl]-2-oxazolidinone (0.28 g, 0.54 mmol) in tetrahydrofuran (10 ml) and 0.5N lithium hydroxide (5 ml) was stirred at 0°C for 3 hours. The mixture was acidified with 1N HCl, diluted with water and extracted with ethyl acetate (3X). The combined extracts were washed with brine, dried over magnesium sulfate and concentrated. The product was isolated by flash chromatography (hexanes/ethyl acetate/acetic acid, 15:5:1) as a white solid, m.p. 96-97°C. $[\alpha]_D -1.0^\circ$ (c 1.76, CHCl₃).

The following compounds were prepared by the same sequence from the appropriate starting materials and reagents.

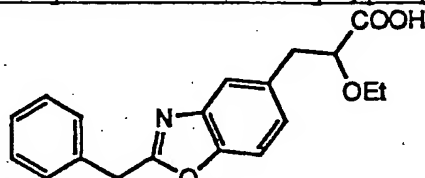
(S)-3-{4-[2-(2-Aminophenyl)]ethoxyphenyl}-2-phenoxypropanoic acid, m.p. 100-103°C. $[\alpha]_D -9.7^\circ$ (c 1.17, CHCl₃).

(S)-3-{4-[2-(4-Benzoyloxyphenyl)]ethoxyphenyl}-2-phenoxypropanoic acid, m.p. 103-105°C. $[\alpha]_D +7.60^\circ$ (c 1.13, CDCl₃).

(R)-3-{4-[2-(4-Benzoyloxyphenyl)]ethoxyphenyl}-2-phenoxypropanoic acid, m.p. 103-105°C. $[\alpha]_D -8.16^\circ$ (c 1.93, CDCl₃).

-64-

(S)-3-(4-[2-(4-Benzyloxyphenyl)]ethoxyphenyl)-2-ethoxypropanoic acid (oil). $[\alpha]_D +5.82^\circ$ (c 0.55, CDCl_3).

EXAMPLE 262-Ethoxy-3-(2-benzyl-5-benzoxazolyl)propanoic acid

- 5 A. 3-(4-Benzyloxy-3-nitrophenyl)-2-ethoxypropane-nitrile. This compound was prepared in 3 steps from 4-benzyloxy-3-nitrobenzaldehyde according to the procedure described in Example 18.
- 10 B. 3-(3-Amino-4-hydroxyphenyl)-2-ethoxypropane-nitrile. A solution of 3-(4-benzyloxy-3-nitrophenyl)-2-ethoxypropanenitrile (0.54 g, 1.7 mmol) in ethanol (25 ml) and acetic acid (75 ml) containing 10% palladium on carbon (0.40 g) was hydrogenated at 45 psi for 1 hour. The catalyst was filtered and the solution concentrated. The
- 15 residue was treated with 5% sodium bicarbonate (100 ml) and extracted with ethyl acetate (3 X 100 ml). The combined extracts were washed with water (2 X 100 ml) and brine (100 ml), dried over sodium sulfate and concentrated. The product was isolated by column
- 20 chromatography (silica gel, 2% methanol in chloroform) as a solid (0.20 g, m.p. 114-115°C)
- 25 C. 2-Ethoxy-3-(4-hydroxyphenyl-3-benzamido)propane-nitrile. A mixture of 3-(3-amino-4-hydroxyphenyl)-2-ethoxypropanenitrile (0.26 g, 1.2 mmol), phenylacetic acid (0.17 g, 1.2 mmol) and dicyclohexylcarbodiimide (0.25 g, 1.2 mmol) in dimethylformamide (0.5 ml) and tetrahydro-
- 30 furan (15 ml) was stirred at room temperature for 14 hours. The solution was concentrated, the residue taken up in ethyl acetate (75 ml), this mixture was filtered and the filtrate was washed with water (3 X 25 ml) and brine (25 ml), dried over sodium sulfate and concentrated. The

-65-

product was isolated by column chromatography (silica gel, chloroform) as an oil (0.21 g).

D. 2-Ethoxy-3-(2-benzyl-5-benzoxazolyl)propane-nitrile. A solution of 2-ethoxy-3-(4-hydroxyphenyl-3-benzamido)propanenitrile (83 mg, 0.26 mmol) and pyridinium p-toluenesulfonate (15 mg, 63 mmol) in xylenes (10 ml) was heated to reflux for 9 hours, then cooled, diluted with ethyl acetate (65 ml), washed with water (3 X 25 ml) and brine (25 ml), dried over sodium sulfate and concentrated. The product was isolated by column chromatography (silica gel, chloroform) as a yellow oil that solidified on standing (50 mg).

E. 2-Ethoxy-3-(2-benzyl-5-benzoxazolyl)propanoic acid. 2-Ethoxy-3-(2-benzyl-5-benzoxazolyl)propanenitrile was hydrolyzed as described in Example 18.

HRMS: Calc. 325.1314
Found 325.1288

The following compounds were prepared by the same sequence from the appropriate starting materials and reagents.

3-[2-(4-Benzyloxybenzyl)-5-benzoxazolyl]-2-ethoxypropanoic acid.

HRMS: Calc. 431.1738
Found 431.1732

25 2-Ethoxy-3-[2-(5-methyl-2-phenyl-4-oxazolylmethyl)-5-benzoxazolyl]propanoic acid.

HRMS: Calc. 406.1533
Found 406.1528

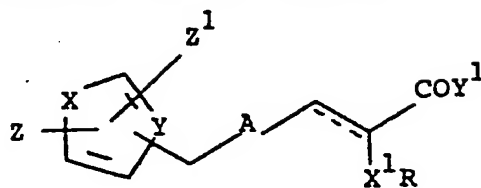
2-Ethoxy-3-[2-(2-pyridylmethyl)-5-benzoxazolyl]propanoic acid.

HRMS: Calc. 326.1270
Found 326.1266

-66-

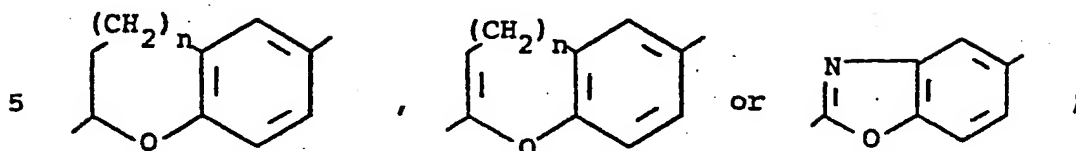
CLAIMS

1. A compound of the formula



wherein:

A is



n is 0 or 1;

--- represents a bond or no bond;

R is C1 to C8 alkyl, C3 to C7 cycloalkyl, C3 to C8 alkenyl, C3 to C8 alkynyl, phenyl, C7 to C8 phenylalkyl, C2 to C8 alkanoyl, or one of said groups mono- or disubstituted with C1 to C3 alkyl, trifluoromethyl, hydroxy, C1 to C3 alkoxy, fluoro or chloro;

X is S, O, NR², -CH=CH-, -CH=N- or -N=CH-;

R² is hydrogen, C1 to C3 alkyl, phenyl or benzyl;

15 Y is CH or N;

Z is hydrogen, C1 to C7 alkyl, C3 to C7 cycloalkyl, phenyl, or phenyl mono- or disubstituted with C1 to C3 alkyl, trifluoromethyl, C1 to C3 alkoxy, phenyl, phenoxy, benzyl, benzyloxy, fluoro or chloro;

20 X¹ is O, S, SO or SO₂;

Y¹ is hydroxy, C1 to C3 alkoxy, phenoxy, benzyloxy, amino, C1 to C4 alkanoylamino, C1 to C4 alkanesulfonylamino, benzenesulfonylamino, naphthalenesulfonylamino, di(C1 to C3 alkyl)aminosulfonylamino, or one of said groups mono- or disubstituted with C1 to C3 alkyl, trifluoromethyl, hydroxy, C1 to C3 alkoxy, fluoro or chloro; and

Z¹ is hydrogen or C1 to C3 alkyl;

a pharmaceutically acceptable cationic salt thereof when Y¹ is hydroxy; or

a pharmaceutically acceptable acid addition salt thereof when the compound contains a basic nitrogen atom.

-67-

2. A compound according to Claim 1 wherein:

--- represents no bond;

X is O and Y is N, together forming an oxazol-4-yl group;

5 Z is phenyl, substituted at the 2-position of the oxazole ring; and

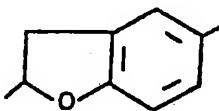
Z¹ is methyl, substituted at the 5-position of the oxazole ring.

3. A compound according to Claim 2 wherein:

10 X¹ is S;

Y¹ is hydroxy;

A is



; and

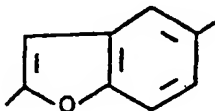
R is C1 to C4 alkyl, phenyl or benzyl.

15 4. A compound according to Claim 2 wherein:

X¹ is O;

Y¹ is hydroxy;

A is



; and

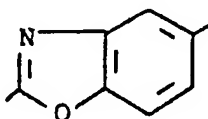
20 R is C1 to C4 alkyl, phenyl or benzyl.

5. A compound according to Claim 2 wherein:

X¹ is O;

Y¹ is hydroxy;

A is



25 ; and

R is C1 to C4 alkyl, phenyl or benzyl.

-68-

6. A compound according to Claim 1 wherein:

--- represents no bond;

X is $-\text{CH}=\text{CH}-$;

Y is $-\text{CH}-$;

5 Z¹ is hydrogen;

X¹ is O; and

Y¹ is hydroxy.

7. A compound according to Claim 6 wherein:

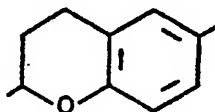
Z is hydrogen, benzyloxy or *m*-fluorobenzyloxy; and

10 R is C1 to C4 alkyl, phenyl or benzyl.

8. A compound according to Claim 7 wherein:

Z is benzyloxy or *m*-fluorobenzyloxy; and

A is

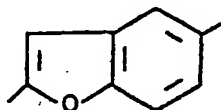


15 9. A compound according to Claim 8 wherein Z is 4-benzyloxy or 4-*m*-fluorobenzyloxy.

10. A compound according to Claim 7 wherein:

Z is 4-benzyloxy; and

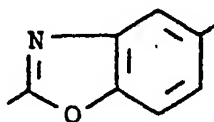
A is



20

11. A compound according to Claim 7 wherein R:

A is



; and

R is C1 to C4 alkyl, phenyl or benzyl.

-69-

12. A compound according to Claim 1 wherein:

--- represents no bond;

X is -CH=CH- and Y is N, together forming a 2-pyridyl group;

5 Z is hydrogen;

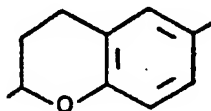
X' is O; and

Y' is hydroxy.

13. A compound according to Claim 12 wherein:

10 Z' is methyl, substituted at the 5-position of the pyridine ring;

A is



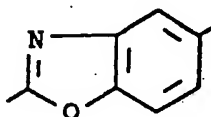
; and

R is phenyl.

14. A compound according to Claim 12 wherein:

15 Z' is hydrogen;

A is



; and

R is ethyl.

15. A compound according to Claim 1 wherein:

20 --- represents a bond;

X is O and Y is N, together forming an oxazol-4-yl group;

Z is phenyl, substituted at the 2-position of the oxazole ring; and

25 Z' is methyl, substituted at the 5-position of the oxazole ring.

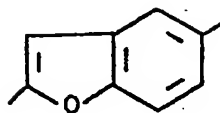
-70-

16. A compound according to Claim 15 wherein:

X^1 is O;

Y^1 is NH_2 ;

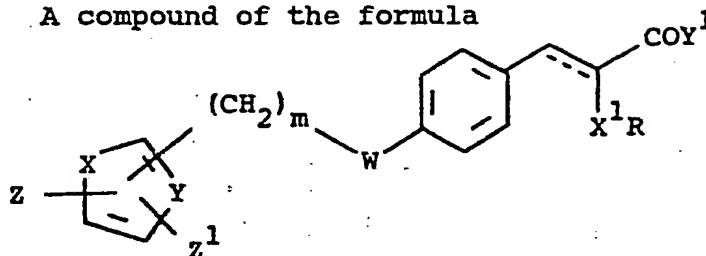
A is



; and

R is phenyl.

17. A compound of the formula



wherein:

W is O, CO, CH_2 , CHOH or $-CH=CH-$;

10 m is 0, 1 or 2;

--- represents a bond or no bond;

R is C1 to C8 alkyl, C3 to C7 cycloalkyl, C3 to C8 alkenyl, C3 to C8 alkynyl, phenyl, C7 to C8 phenylalkyl, C2 to C8 alkanoyl, or one of said groups mono- or
15 disubstituted with C1 to C3 alkyl, trifluoromethyl, hydroxy, C1 to C3 alkoxy, fluoro or chloro;

X is S, O, NR^2 , $-CH=CH-$, $-CH=N-$ or $-N=CH-$;

R^2 is hydrogen, C1 to C3 alkyl, phenyl or benzyl;

Y is CH or N;

20 Z is hydrogen, C1 to C7 alkyl, C3 to C7 cycloalkyl, phenyl, or phenyl mono- or disubstituted with C1 to C3 alkyl, trifluoromethyl, C1 to C3 alkoxy, phenyl, phenoxy, benzyl, benzyloxy, fluoro or chloro;

X^1 is O, S, SO or SO_2 ;

25 Y^1 is hydroxy, C1 to C3 alkoxy, phenoxy, benzyloxy, amino, C1 to C4 alkanoylamino, C1 to C4 alkanesulfonylamino, benzenesulfonylamino, naphthalenesulfonylamino, di(C1 to C3 alkyl)aminosulfonylamino, or one of said groups mono- or disubstituted with C1 to C3 alkyl, tri-

-71-

fluoromethyl, hydroxy, C1 to C3 alkoxy, fluoro or chloro;
and

Z¹ is hydrogen or C1 to C3 alkyl;

a pharmaceutically acceptable cationic salt thereof

5 when Y¹ is hydroxy; or

a pharmaceutically acceptable acid addition salt
thereof when the compound contains a basic nitrogen atom.

18. A compound according to Claim 17 wherein:

m is 2; and

10 X is O and Y is N, together forming an oxazol-4-yl
group.

19. A compound according to Claim 18 wherein:

W is O or CO;

m is 2;

15 R is C1 to C4 alkyl or C2 to C8 alkanoyl;

Z is phenyl, substituted at the 2-position of the
oxazole ring;

X¹ is S or O;

Y¹ is OH; and

20 Z¹ is methyl, substituted at the 5-position of the
oxazole ring.

20. A compound according to Claim 19 wherein:

W is O;

R is methyl; and

25 X¹ is S.

21. A compound according to Claim 19 wherein:

W is O;

--- represents no bond;

R is acetyl; and

30 X¹ is S.

-72-

22. A compound according to Claim 19 wherein:
W is CO;
--- represents a bond;
R is methyl; and
5 X¹ is S.
23. A compound according to Claim 19 wherein:
W is CO;
--- represents no bond;
R is ethyl; and
10 X¹ is O.
24. A compound according to Claim 17 wherein:
m is 2;
X is -CH=CH-; and
Y is -CH-.
- 15 25. A compound according to Claim 24 wherein:
W is O;
--- represents no bond;
X¹ is O;
Y¹ is OH; and
20 Z¹ is hydrogen.
26. A compound according to Claim 25 wherein:
R is C1 to C4 alkyl, phenyl or benzyloxy; and
Z is hydrogen, benzyloxy or fluorobenzyloxy.
- 25 27. A compound according to Claim 26 wherein:
R is phenyl; and
Z is hydrogen, 4-benzyloxy or 4-*m*-fluorobenzyloxy.
28. A compound according to Claim 26 wherein:
R is methyl or ethyl; and
Z is 4-benzyloxy or 4-*m*-fluorobenzyloxy.

-73-

29. A compound according to Claim 26 wherein:

R is benzyloxy; and

Z is 4-benzyloxy.

30. A compound according to Claim 17 wherein:

5 m is 3; and

X is -CH=CH- and Y is N, together forming a 2-pyridyl group.

31. A compound according to Claim 30 wherein:

W is O;

10 --- represents no bond;

R is C1 to C4 alkyl;

Z is ethyl, substituted at the 5-position of the pyridyl ring;

X¹ is O;

15 Y¹ is OH; and

Z¹ is hydrogen.

32. A compound according to one of Claims 1, 2 or 17 wherein --- represents no bond and which is optically active.

20 33. A pharmaceutical composition for use in a hyperglycemic mammal which comprises a blood glucose lowering amount of a compound according to Claim 1, 4, 8, 17 or 26.

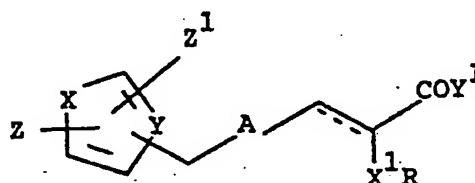
25 34. A method of lowering the blood glucose in a hyperglycemic mammal which comprises administering to said mammal a blood glucose lowering effective amount of a compound according to Claim 1, 4, 8, 17 or 26.

30 35. A pharmaceutical composition for use in a hypercholesterolemic mammal which comprises a blood cholesterol lowering amount of a compound according to Claim 1, 4, 8, 17 or 26.

-74-

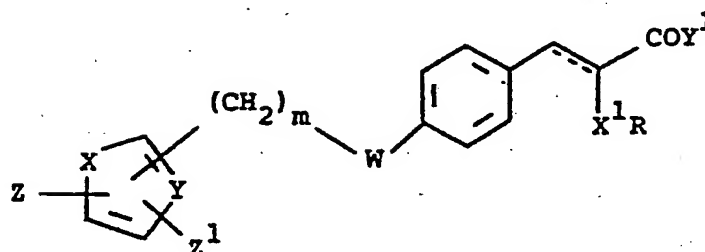
36. A method of lowering the blood cholesterol in a hypercholesterolemic mammal which comprises administering to said mammal a blood cholesterol lowering effective amount of a compound according to Claim 1, 4, 8, 17 or 26.

37. A process for preparing a compound of the formula



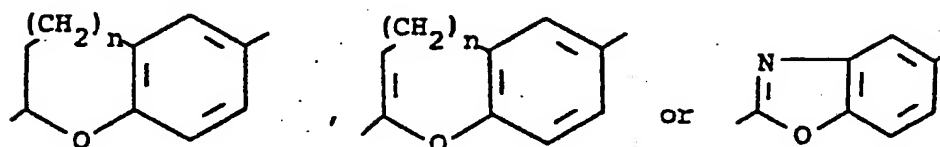
I

or



II

wherein A is



n is 0 or 1;

m is 0, 1 or 2;

--- represents a bond or no bond;

R is C1 to C8 alkyl, C3 to C7 cycloalkyl, C3 to C8 alkenyl, C3 to C8 alkynyl, phenyl, C7 to C8 phenylalkyl, C2 to C8 alkanoyl, or one of said groups mono- or disubstituted with C1 to C3 alkyl, trifluoromethyl, hydroxy, C1 to C3 alkoxy, fluoro or chloro;

W is O, CO, CH₂, CHOH or -CH=CH-;

-75-

X is S, O, NR^2 , $-\text{CH}=\text{CH}-$, $-\text{CH}=\text{N}-$ or $-\text{N}=\text{CH}-$;

R^2 is hydrogen, C1 to C3 alkyl, phenyl or benzyl;

Y is CH or N;

Z is hydrogen, C1 to C7 alkyl, C3 to C7 cycloalkyl,
 5 phenyl, or phenyl mono- or disubstituted with C1 to C3
 alkyl, trifluoromethyl, C1 to C3 alkoxy, phenyl, phenoxy,
 benzyl, benzyloxy, fluoro or chloro;

X^1 is O, S, SO or SO_2 ;

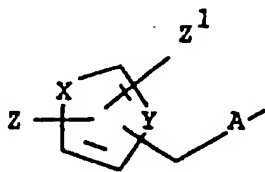
Y^1 is hydroxy, C1 to C3 alkoxy, phenoxy, benzyloxy,
 10 amino, C1 to C4 alkanoylamino, C1 to C4 alkanesulfonyl-
 amino, benzenesulfonylamino, naphthalenesulfonylamino,
 di(C1 to C3 alkyl)aminosulfonylamino, or one of said
 groups mono- or disubstituted with C1 to C3 alkyl,
 trifluoromethyl, hydroxy, C1 to C3 alkoxy, fluoro or
 15 chloro; and

Z^1 is hydrogen or C1 to C3 alkyl;

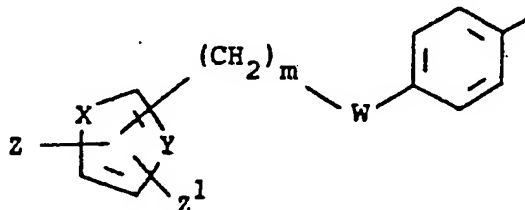
a pharmaceutically acceptable cationic salt thereof
 when Y^1 is hydroxy; or

a pharmaceutically acceptable acid addition salt
 20 thereof when the compound contains a basic nitrogen atom,
 comprising:

(a) when --- represents a bond, X^1 is S and Y^1 is
 hydroxy, an aldehyde of the formula $\text{R}'\text{CHO}$, wherein R' is



when a compound of Formula I is desired, or is



25 when a compound of Formula II is desired, wherein m, A,
 W, X, Y, Z and Z^1 are as defined above, is condensed with
 thiazolidine-4-one-2-thione in the presence of a
 secondary amine in a reaction-inert solvent and the

-76-

resulting thiazolidine is transformed into the final product by reaction with a compound of the formula ROH, wherein R is as defined above;

(b) when --- represents a bond and X^1 is O, a
5 compound of the formula $CH_2=COR-CN$ or $CH_2=COR-COY^1$, wherein R and Y^1 are as defined above except that Y^1 is not hydroxy, is converted to its sodium salt by reaction with NaH in a reaction-inert solvent, the resulting salt is condensed with an aldehyde of the formula $R'CHO$, where R'
10 is as defined above, to form a compound of the formula $R'CH=C(OR)CN$ or $R'CH=C(OR)COY^1$, respectively, which compound is then, if of the formula $R'CH=C(OR)COY^1$, optionally hydrolyzed to the corresponding acid, or, if of the formula $R'CH=C(OR)CN$, is converted to a compound
15 of the formula $R'CH=C(OR)COY^1$ or to the corresponding acid;

(c) when --- represents no bond, the compounds prepared by (a) and (b) above are reduced to the corresponding product;

20 (d) when --- represents no bond and X^1 is S, a nitrile of the formula $R'CH_2CH(X^2)CN$, or an ester of the formula $R'CH_2CH(X^2)COOR^1$, wherein R' is as defined above, X^2 is a nucleophilically displaceable group and R^1 is an ester forming group, is transformed into the corresponding
25 desired product by nucleophilic displacement of the group X^2 with RS^- , wherein R is as defined above, with the concurrent or subsequent conversion of the nitrile or ester group to the group $-COY^1$;

(e) when --- represents no bond and X^1 is O, an α -
30 hydroxy ester of the formula $R'CH_2CHOHCOOR^1$ or a cyanhydrin of the formula $R'CH_2CH(OR^2)CN$, wherein R' , R^1 and R^2 are as defined above, is converted to an ester of the formula $R'CH_2CH(OR)COOR^1$ or the corresponding acid of the formula $R'CH_2CH(OR)COOH$.

-77-

38. A process according to Claim 37 wherein:

in (a), said secondary amine is piperidine or pyrrolidine, said reaction-inert solvent is ethanol and said condensation reaction occurs at between 40 and
5 100°C;

in (b), said reaction-inert solvent is dimethylformamide, said reaction with NaH occurs at between 25 and 60°C, said condensation reaction occurs at between 50 and 100°C and said hydrolyzation reaction
10 takes place under aqueous basic conditions;

in (c), said catalyst is Pd/C, Rh/C or Rh(Ph₃P)₃Cl, said reaction-inert solvent is ethanol, and said hydrogenation takes place at a temperature between ambient temperature and 80°C and a pressure between
15 ambient pressure and 125 psig;

in (d), said nucleophilically displaceable group is I, Cl, Br or OSO₂CH₃, R¹ is C1 to C3 alkyl, Y¹ is alkoxy, and said nitrile conversion takes place by reacting the nitrile with dry HCl in an excess of the corresponding
20 alkanol at a temperature between 15 and 45°C; or

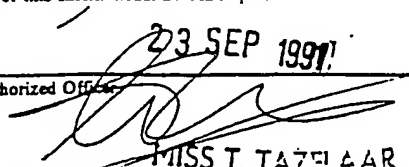
in (e), said α-hydroxy ester conversion comprises reacting said ester, when RO is an ester, by reaction with an activated acid in the presence of at least one equivalent of a tertiary amine; or, when RO is an ether,
25 by reaction with NaH under anhydrous conditions in a reaction-inert solvent to form the sodium salt thereof, which in turn is either coupled with a mesylate ester or halide under anhydrous nucleophilic displacement conditions to form said corresponding ester or under
30 hydrous nucleophilic displacement conditions to form said corresponding acid, and said cyanhydrin conversion comprises conversion of the nitrile group to the corresponding acid by the action of NaOH in an aqueous solvent or to the corresponding ester by the action of
35 dry HCl in an excess of an alcohol of the formula R¹OH, wherein R¹ is C1 to C3 alkyl.

-78-

39. A process according to Claim 38 wherein, in (e), said activated acid is an acid chloride or mixed anhydride.

INTERNATIONAL SEARCH REPORT

International Applica. No. PCT/US 91/03858

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) and to both National Classification and IPC Int.Cl.5 C 07 D 263/24 A 61 K 31/425 C 07 D 413/06 C 07 D 311/58 A 01 N 31/35 C 07 D 263/56 C 07 C 59/64 C 07 C 69/612		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl.5	C 07 D 263/00 C 07 D 413/00 C 07 D 311/00 C 07 C 59/00	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0177353 (TAKEDA) 9 April 1986, see claims -----	1,17,33 ,35
A	EP,A,0299620 (BEECHAM) 18 January 1989, see claims -----	1,17,33 ,35
A	WO,A,8908651 (PFIZER INC.) 21 September 1989, see claims (cited in the application) -----	1,17,33 ,35
A	WO,A,8908650 (PFIZER INC.) 21 September 1989, see claims (cited in the application) -----	1,17,33 ,35
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
28-08-1991	23 SEP 1991	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	 MISS T. TAZELAAR	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim numbers ^{*)} because they relate to subject matter not required to be searched by this Authority, namely:
 → 34, 36
 See PCT-Rule 39.1 (iv): methods for treatment of the human or animal body by surgery or therapy as well as diagnostic methods
2. ☐ Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:
3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this International application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.

US 9103858

SA 48615

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 17/09/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0177353	09-04-86	WO-A- 8602073	10-04-86
		WO-A- 8606069	23-10-86
		AU-B- 583537	04-05-89
		AU-A- 4817685	10-04-86
		CA-A- 1263655	05-12-89
EP-A- 0299620	18-01-89	AU-A- 1767588	15-12-88
		JP-A- 1013088	17-01-89
WO-A- 8908651	21-09-89	EP-A- 0332332	13-09-89
WO-A- 8908650	21-09-89	EP-A- 0332331	13-09-89

